Medical
Faxon

The Journal of Pediatrics

VOL. 39 JULY, 1951 No. 1

ANTIBIOTIC TREATMENT OF PERTUSSIS

COMPARISON OF PENICILLIN, AUREOMYCIN, CHLORAMPHENICOL, AND TERRAMYCIN IN 150 CASES

LLOYD N. HAZEN, M.D., GEORGE GEE JACKSON, M.D.,* CHANG, SHIH-MAN, M.D., EDWIN H. PLACE, M.D., AND MAXWELL FINLAND, M.D.

BOSTON, MASS.

IN A previous study carried out in this hospital, Chang and associates[1] reported that when aureomycin was given by mouth to patients with pertussis, clinical improvement began soon after this treatment was started and continued steadily in most cases. The number, severity, and duration of paroxysms were significantly reduced in the aureomycin-treated patients as compared with similar and contemporary cases receiving no antibiotic therapy. Nasopharyngeal cultures became negative for *Hemophilus pertussis* soon after aureomycin was started, and these organisms could then no longer be obtained from such cultures if the treatment was continued for ten days, but did reappear in some patients after treatment for only five days.

The present communication deals with clinical, bacteriological, and some preliminary serological observations on the relative effects of penicillin, aureomycin, chloramphenicol, and terramycin in 150 cases of whooping cough with positive cultures for *H. pertussis*. This study was undertaken, in part, because the possibility could not be excluded that some, if not all, of the clinical improvement observed in the previous study was due to the influence of the aureomycin on secondary infections of the respiratory tract; penicillin was, therefore, used to control this aspect. It was also desired to observe and compare the effects of the other antibiotics.

MATERIALS AND METHODS

Selection of Cases.—The 150 patients included in this study were observed during the twelve months from December, 1949, through November, 1950. More than one-half of them were admitted during the months of July, August, and September, 1950, but some patients were admitted during each of the twelve months of the study. They were all hospitalized on one ward where nurses who had been indoctrinated in the methods of the study were in constant attendance. The patients were segregated only according to age, but not according to the therapy used.

From the South Department and the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Aided by grants from the United States Public Health Service and from the William F. Milton Fund.

*Milton Fellow, Harvard Medical School.

Most of the patients entered the hospital in the early paroxysmal stage of pertussis, although some siblings of patients with whooping cough were admitted while still in the catarrhal stage. Patients who were severely ill with characteristic symptoms of whooping cough when first seen were admitted directly to the ward and treatment was begun soon after a nasopharyngeal culture was taken and before the result was reported. In such cases, if the pretreatment and subsequent cultures failed to yield *H. pertussis*, the case was later excluded from the series. However, the clinical condition of many patients permitted a delay in instituting therapy for one or two days until the results of the cultures were known, and the cases were then admitted to the study. Some patients with cough and catarrhal symptoms who were contacts of known cases of whooping cough were first seen as out-patients and cultures were made at that time; they were later admitted to the hospital only after *H. pertussis* was identified in their nasopharyngeal cultures.

*Selection of Therapeutic Agents.**—The patients under 1 year of age were segregated from those over 1 year of age and the antibiotic to be used in each patient was determined by rotation within these age groups. When one of the antibiotics was not available, the patients were placed in the penicillin group instead and some of them were not treated at the time; this accounts for the excess of patients in the penicillin group. There were four patients in whom penicillin was not started until a week or longer after admission, and two others are included in the penicillin series although the antibiotic was not given; one of the latter patients was entirely asymptomatic when the result of the culture was reported.

Dosage.—All of the antibiotics were given by mouth; each patient was treated for ten days and received 60 mg. per kilogram per day in four doses. In seven patients, however, some of the penicillin was given intramuscularly and for longer periods either because of the presence of febrile complications or because of failure of the patient to improve on oral therapy. The oral penicillin was given either as small compressed tablets, each containing 60 mg. (100,000 units) of crystalline potassium penicillin G, or the appropriate dose was dissolved in the feedings. Aureomycin hydrochloride and chloramphenicol were given as capsules, each containing either 50 or 250 mg. Terramycin hydrochloride was given either in capsules or as a powder suspended in a flavored syrup.

Laboratory Studies.—Cultures of nasopharyngeal swabs were made in each case according to the method recommended by Bradford, Day, and Berry[2] at the time of admission; these were repeated on each of the next two days, and two or three times each week thereafter until the patient was discharged from the hospital. The swabs were streaked promptly on Verway's agar medium[3] containing 12 per cent defibrinated sheep's blood. A drop of saline containing 1,000 units of penicillin per milliliter was placed in the center of each plate. The swab was streaked first over a peripheral portion of the plate to determine the

*We are indebted to Dr. Stanton M. Hardy of the Lederle Laboratories for the supply of aureomycin, to Dr. E. A. Sharp of Parke, Davis & Co., for the chloramphenicol (Chloromycetin), and to Dr. Gladys L. Hobby of Chas. Pfizer & Co., for the terramycin used in this study.

flora uninhibited by penicillin; it was then streaked back and forth through the penicillin solution over the rest of the surface of the plate. This permitted growth of *H. pertussis* while inhibiting the penicillin sensitive mouth flora. The plates were incubated at 37° C. and examined daily for three days. *H. pertussis* was identified by colony morphology, staining characteristics, and by a slide agglutination with specific antiserum.

Blood for serologic studies was collected early and late in the hospital course of some of the patients. The serum was separated and stored in a refrigerator until used. Antibody titers were determined in the paired specimens from each case by a macroscopic tube agglutination with serial twofold dilutions of serum in saline. A fresh, formalinized saline suspension prepared from a single recently isolated smooth strain of *H. pertussis* was used; it contained 30 to 300 billion organisms per milliliter. A human serum having a titer of 1:640 was used as a control with each group of tests.* An additional specimen of serum was obtained from some of the patients during follow-up visits and tested in the same manner.

Total white blood cell and differential counts were done on admission and at frequent intervals thereafter. Roentgenograms of the chest were made in each case at the time of admission to the hospital and these were repeated when indicated.

Clinical Data.—In obtaining the history, special attention was paid to prior immunization, previous communicable diseases and exposure to other diseases, as well as to the details and duration of the symptoms of the present illness. The usual clinical observations were made and the number and severity of the paroxysms of cough were charted by the nurse. The severity of each paroxysm was arbitrarily classified as severe, moderate, or mild at the time when it was observed.

*We are indebted to Miss Marion E. Lamb for advice and help with these tests.

ANALYSIS OF CASES

Some of the relevant data in the cases are analyzed in Table I. These and some additional features of the various therapeutic groups may be commented on briefly.

Age.—The patients ranged in age from 4 weeks to 11 years. One-third of them were under 1 year of age and averaged 5.8 months; the average age of the remaining patients was 3⅓ years. In all of the analyses the infants under 1 year of age are considered apart from the children over 1 year of age. The age distribution did not differ significantly among the therapeutic groups.

Previous Immunization.—A history of a completed course of pertussis immunization (together with diphtheria and tetanus immunization) was obtained in forty-seven of the patients over 1 year of age, but in only three of the infants. Six additional infants had received only a single inoculation mostly within a month of the present illness. There was no great preponderance of fully immunized children in any of the therapeutic groups.

Previous Antibiotic Therapy.—Only six patients had received any antibiotic therapy for the present illness prior to admission to the hospital. In each instance the treatment was considered grossly inadequate or had been given long enough prior to entry to

TABLE I. ANALYSIS OF 150 CASES INCLUDED IN THE STUDY

ANTIBIOTIC THERAPY	PENICILLIN	AUREOMYCIN	CHLORAMPHENICOL	TERRAMYCIN
Total number of patients	49	33	37	31
Patients under 1 year of age	18*	12	13	7
Range of age	4 wk.-11 mo.	7 wk.-11 mo.	8 wk.-11 mo.	6 wk.-10 mo.
Average age	*5.3 mo.*	*4.9 mo.*	*6.5 mo.*	*7.3 mo.*
Previously immunized†	1[1]	2[2]	3[2]	3[1]
Average duration before entry (days):				
Cough and catarrh	*11.5*	*11.6*	*9.5*	*9.1*
Paroxysms	*4.0*	*4.1*	*3.1*	*2.9*
Vomiting	*3.5*	*2.8*	*2.0*	*2.4*
Fever (100° F. or over) in first 2 days	8	0	?	2
Estimate of severity:‡				
Severe	9	3	4	2
Moderate	6	7	7	2
Mild	3	2	2	3
Patients over 1 year of age	31	21	24	24
Range of age	12 mo.-11 yr.	15 mo.-7 yr.	14 mo.-7 yr.	13 mo.-8 yr.
Average age	*43 mo.*	*37 mo.*	*37 mo.*	*40 mo.*
Previously immunized	13	8	13	13
Average duration before entry (days):				
Cough and catarrh	*9.0*	*11.0*	*9.0*	*10.4*
Paroxysms	*2.2*	*3.5*	*3.2*	*3.3*
Vomiting	*1.5*	*2.2*	*2.4*	*3.1*
Fever (100° F. or over) in first 2 days	8	4	6	7
Estimate of severity:‡				
Severe	6	5	3	6
Moderate	16	10	9	7
Mild	9	6	12	11

*In four patients penicillin was started one week or longer after entry; two others are included although penicillin was not given.

†Superior numbers indicate number of partially immunized patients included.

‡This estimate was made during the first few days in the hospital and therefore reflects, in part, some of the early effects of the therapy in most of the cases.

permit a bacteriologic and clinical relapse. Penicillin, streptomycin, aureomycin, and chloramphenicol were the agents used.

Duration of Symptoms.—Most of the patients had had coryza with some cough for one to two weeks prior to entry. Paroxysmal cough was first noted only one to two days before admission to the hospital in most patients but some of them had been whooping for a week or more. Vomiting and regurgitation commonly began only after the paroxysmal cough had developed. Among the infants, the average duration of each of these symptoms was about one day longer for those in the penicillin group than for those treated with other antibiotics. Among the children over 1 year of age, the reverse was true; those treated with aureomycin, chloramphenicol, or terramycin had had symptoms for an average of one day longer than those in the penicillin group.

Fever.—About one-fourth of the patients had fever (100° F. or higher) during the first day or two after admission and this was true both among infants and among children over 1 year of age. Fever was present at this time among eight of the eighteen infants in the penicillin group and in none of the aureomycin-treated in-

fants, otherwise the incidence of fever early in the hospital course was similar in each of the therapeutic groups.

Severity of the Disease.—The illness in each patient was classified as severe, moderate, or mild during the first three or four days of observation in the hospital. This classification was based on the personal estimate of the physician in charge and was judged by the general appearance of "toxicity," the number and severity of paroxysms, cyanosis and vomiting, the appetite, and general interest of the patient in his environment. By these criteria 25 per cent of the patients were judged to have severe disease, while in 43 per cent it was moderate, and in 32 per cent it was mild. The proportion of clinically severe cases was greater among infants (36 per cent) than among those over 1 year of age (20 per cent), and it was greater among infants in the penicillin group than in those treated with other antibiotics. Some of the differences noted, however, may have been due to the prompt improvement in the clinical appearance of the latter patients after treatment was instituted.

Leucocyte Counts.—The total white blood count on admission varied between 3,500 and 84,000 per cubic millimeter. In most of the patients it ranged between 10,000 and 30,000, and differential counts showed more than 60 per cent lymphocytes.

X-ray Findings.—Significant roentgenographic abnormalities in the form of patchy areas of density in the lungs were made out in the admission films in only six patients; three were in the penicillin group, one received chloramphenicol, and the other two were treated with terramycin.

RESULTS

Effect of Therapy on Paroxysmal Cough.—The average number of paroxysms per day among all of the patients treated with either aureomycin, chloramphenicol, or terramycin declined more rapidly than it did in the penicillin group (Fig. 1, upper left panel). This difference was quite marked among the infants (right panel) but was not so striking among the older children (lower left panel). When the severity of the paroxysms was also considered and the average daily "cough index" was charted for each group in the same manner, similar differences were observed except that they were somewhat more striking.

It is worth noting in Fig. 1 that each of the curves appears to level off, or even to rise slightly, between the tenth and fourteenth days, that is, during the days immediately following the cessation of treatment. While this effect on the average numbers of paroxysms was not striking, the rebound increase in paroxysmal cough was quite significant in individual cases.

The total duration of paroxysmal cough of any severity, likewise, was longer in the penicillin group than among patients treated with the other antibiotics (Table II). This difference, too, was greater among the infants; the average number of days of whooping among the infants in the penicillin group was 21.8 as compared with 14.5 days among all the infants treated with the other three antibiotics. Among the children over 1 year of age, the corresponding figures were 18.0 days for the penicillin group and 15.0 days for all those treated

with aureomycin, chloramphenicol, or terramycin.

Fever.—As can be seen from Table II, a few of the patients had some fever after antibiotic therapy was started. There were thirteen such patients in the penicillin group; eight of them were under 1 year of age and had a temperature of 100° F. or higher for one to five days, while five of those over 1 year of age had fever, but in only one of them did it last for more than one day after the penicillin was started. Fever was also observed in seven patients after terramycin was begun, but only two of those receiving aureomycin and three who were treated with chloramphenicol had significant temperature rises after the antibiotic was started.

Clinical Response.—A general clinical estimate of the response to therapy was made in each case on the basis of the changes in "toxicity," frequency and severity of paroxysmal cough, cyanosis, vomiting, appetite, and in some instances on the weight changes following the institution of therapy. The beneficial effects were graded as "good," "equivocal," or "none" (Table II). A good clinical response was observed in only four patients, and no effect was noted in more than three-fourths of those in the penicillin group. By contrast, almost two-thirds of the patients treated with aureomycin, chloramphenicol, or terramycin were judged as showing good clinical effects following treatment and only about one in ten either showed no ef-

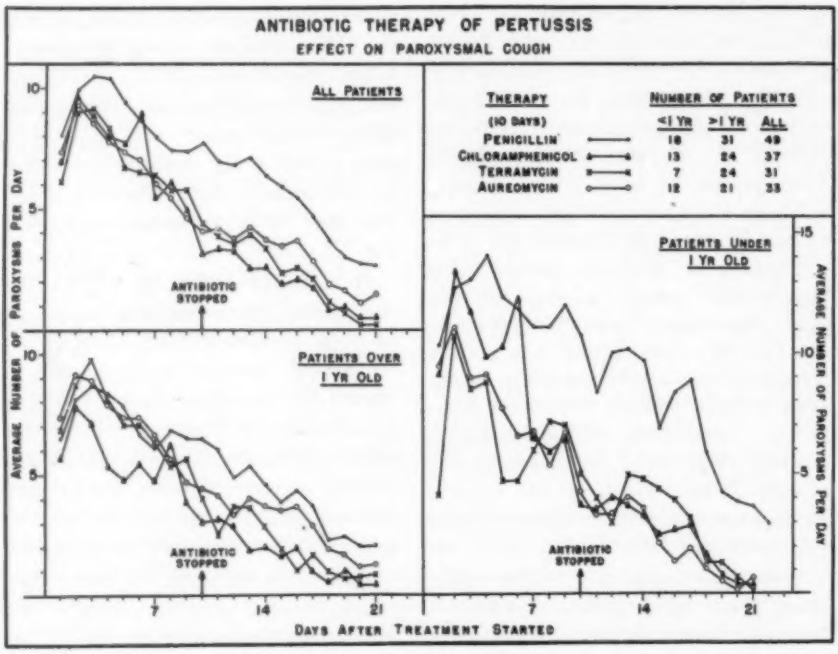

Fig. 1.

fect from these agents or developed some complications during or after this therapy.

There were no deaths among the 150 patients in this study.

pleted. The average number of days in the hospital (Table II) was greater for the patients in the penicillin group than for those treated with other agents. Among the infants the differ-

TABLE II. ANALYSIS OF CLINICAL EFFECTS OF ANTIBIOTIC THERAPY

ANTIBIOTIC AGENT	PENICILLIN	AUREOMYCIN	CHLORAMPHENICOL	TERRAMYCIN
Patients under 1 year of age	18	12	13	7
Paroxysmal cough in the hospital:				
14 days or less	5	5	8	2
15-21 days	4	6	3	4
22-28 days	5	1	0	1
29 days or longer	4	0	2	0
Average number of days	*21.8*	*15.6*	*13.8*	*14.1*
Number with fever after treatment begun	8	0	2	3
Average number of days 100° F. or higher	*3*		*2*	*2*
Average number of hospital days	*22.8*	*15.9*	*17.2*	*18.4*
Number with complications	2*	0	2†	0
Clinical estimate of benefit:				
Good	1	12	10	4
Equivocal	3	0	1	1
None	14	0	2	2
Patients over 1 year of age	31	21	24	24
Paroxysmal cough in the hospital:				
14 days or less	9	6	13	11
15-21 days	14	12	8	10
22-28 days	6	2	2	3
29 days or longer	2	1	1	0
Average number of days	*18.0*	*17.4*	*13.5*	*14.5*
Number with fever after treatment begun	5	2	1	4
Average number of days 100° F. or higher	*1½*	*3½*	*1*	*3*
Average number of hospital days	*19.2*	*18.7*	*16.3*	*16.8*
Number with complications	1‡	3§	0	3‖
Clinical estimate of benefit:				
Good	3	10	16	19
Equivocal	4	8	5	5
None	24	3	3	0

*Bronchopneumonia on admission in 1 case and 4 weeks after treatment in the other.

†Bronchopneumonia before treatment in 1, clinical and bacteriologic relapse in 1.

‡Bronchopneumonia on admission.

§Bronchopneumonia on admission, 1 case; clinical and bacteriologic relapse with bronchopneumonia, 1 case; staphylococcal scarlet fever during treatment, 1 case.

‖Bronchopneumonia on admission, 2 cases; staphylococcal scarlet fever during treatment, 1 case.

Duration of Hospitalization.—The length of the hospital stay was influenced in some individual cases by the requirements of the study or by the desires of the parents. Some patients were kept somewhat longer than necessary until adequate clinical and bacteriologic observations were com-

ence was about 6 days (the average was 22.8 days for the penicillin group and 16.9 days for all the others) while for those over 1 year of age it was only 1½ days (the average for the penicillin group was 19.2 days and for those treated with aureomycin, chloramphenicol, or terramycin it was 17.7 days).

TABLE III. RESULTS OF NASOPHARYNGEAL CULTURES FOR H. PERTUSSIS

DAYS AFTER TREATMENT BEGUN	PENICILLIN			AUREOMYCIN			CHLORAMPHENICOL			TERRAMYCIN		
	PATIENTS CULTURED	NUMBER POSITIVE	PER CENT POSITIVE	PATIENTS CULTURED	NUMBER POSITIVE	PER CENT POSITIVE	PATIENTS CULTURED	NUMBER POSITIVE	PER CENT POSITIVE	PATIENTS CULTURED	NUMBER POSITIVE	PER CENT POSITIVE
Before	47	44	94	32	32	100	37	37	100	31	31	100
1-2	45	41	91	31	25	83	35	35	100	29	28	97
3-4	35	29	83	24	3	13	36	3	8	25	2	8
5-7	42	32	72	25	1*	4	23	0	0	22	0	0
8-14	46	31	67	32	1*	3	37	0	0	29	0	0
15-21	28	8	29	19	2*†	11	20	0	0	16	0	0
22-28	9	1	11	2	1*		3	1‡		4	0	

*Patient R. G. (Fig. 3).
†Patient J. S. B. (Fig. 3).
‡Patient T. M. (Fig. 3).

Complications.—There were eight patients with bronchopneumonia; six of them already had abnormal roentgenographic findings at the time of admission. One infant developed bronchopneumonia four weeks after treatment with penicillin and another developed this complication during aureomycin therapy which was associated with excessive vomiting (J. S. B., Fig. 3). No other significant pulmonary complications were observed during the course of therapy or later in the hospital stay. Bacteriologic and clinical relapse occurred after apparent improvement in one of the patients of each of the therapeutic groups. Two patients developed staphylococcal scarlet fever, one during treatment with aureomycin and the other during terramycin therapy. Details of some of these cases will be presented under "treatment failures."

Effect on Leucocyte Counts.—The total leucocyte counts and the per cent of lymphocytes showed a decreasing trend during the period of hospitalization. However, neither of these measurements seemed to correlate with the clinical progress of the patients. There were no significant differences in the total white blood cell or differential counts among the patients treated with the different antibiotics.

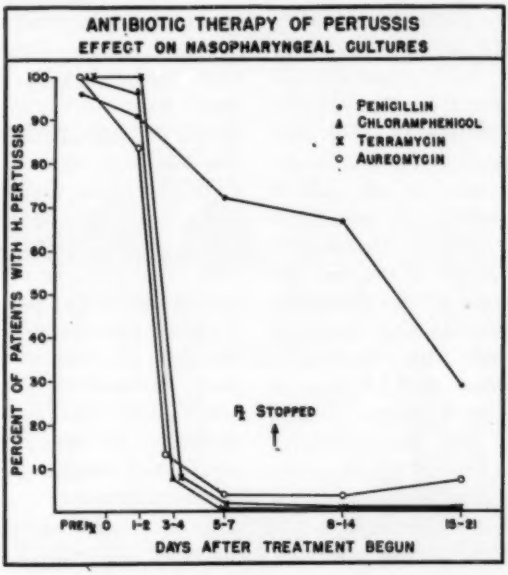

Fig. 2.

Bacteriologic Effects.—The results of nasopharyngeal cultures for *H. pertussis* before and after treatment with the various antibiotics are summarized in Table III and in Fig. 2. *H. pertussis* persisted in these cultures during the first two days of treatment with each of the four antibiotics. On and after the third day, however, this organism was only rarely recovered from the nasopharyngeal cultures of the patients who were treated with either

aureomycin, chloramphenicol, or terramycin. The three patients from whom *H. pertussis* was recovered after the fourth day of treatment with aureomycin or chloramphenicol are discussed below under "treatment failures." The per cent of patients in the penicillin group who yielded positive cultures declined slowly over a period of four weeks.

Antibody Response.—Serums were obtained shortly after admission and again two to three weeks later in forty patients, ten of them, including two or three infants, being selected arbitrarily from among those treated with each of the four antibiotics. The titer of *H. pertussis* agglutinins was determined simultaneously in the paired sera from each patient. A fourfold or greater rise in titer in the second serum over that found in the first one was obtained in six of the penicillin-treated patients but in only one each among those treated with chloramphenicol and terramycin and in none of those treated with aureomycin. The average titer in the ten penicillin-treated patients rose 3.5-fold while that of the remaining thirty patients rose only 1.4-fold, the increases in the average titers being similar for each of the groups treated with the other three antibiotics.

An additional specimen of serum was obtained two to four months after discharge from the hospital in twenty-five of these forty patients, including seven who had been treated with terramycin and six from among each of the ten who had been treated with the other three antibiotics. Further increases in titers were noted in three of the six penicillin-treated patients, while sixteen of the nineteen who had been treated with either aureomycin, chloramphenicol, or terramycin showed significantly higher titers in these later convalescent bloods. The average increase in titer in these late bloods over that of the original acute-phase serum was 5.4-fold among the six penicillin-treated patients and 3.5-fold in the nineteen patients who had been treated with one of the other three antibiotics.

Drug Toxicity and Treatment Failures.—Generally speaking all of the agents used in treatment were well tolerated. Gastrointestinal symptoms were much less than had been anticipated from the experience with these drugs in adult patients even though the dose administered was greater on a weight basis than that commonly given to adults. Vomiting or regurgitation occurred to a greater extent early in the course of therapy and in association with severe paroxysmal coughing than was observed in the latter part of therapy. As the paroxysms decreased in frequency and severity so also did the vomiting in most patients. In some infants normal or accelerated weight gain began again during treatment.

In a very few patients vomiting was apparently increased by the medication and the bouts of vomiting became associated with the ingestion of food or medicine. In the upper left-hand panel of Fig. 3 is presented one such case which is associated with bacteriologic relapse after treatment.

This child, J. S. B., was severely ill and vomited frequently with paroxysms of coughing. During the first few days after admission to the hospital the paroxysmal cough became more severe and the patient developed fever and bilateral bronchopneumonia. After ten days of treatment with aureomycin the paroxysms had de-

creased in number and severity and the bronchopneumonia was beginning to clear, but vomiting persisted. After treatment was omitted there was a recurrence of severe paroxysms and the nasopharyngeal cultures later again became positive for *H. pertussis*. This case was the only one with bacteriologic relapse observed among the thirty-three patients who received aureomycin therapy.

This patient, R. T., had mild pertussis but the nasopharyngeal culture taken on admission yielded a moderate number of hemolytic *Staph. aureus* in addition to *H. pertussis*. After terramycin therapy was started hemolytic *Staph. aureus* was obtained from the cultures in increasing abundance. On the third day of treatment the temperature rose to 101° F. and subsequently a generalized scarlatiniform

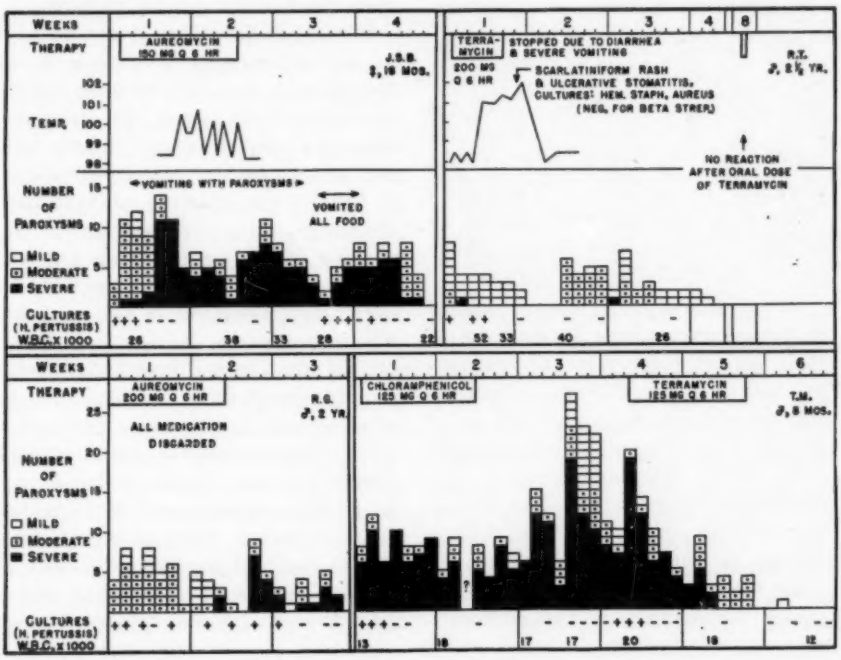
WEEKS
THERAPY
AUREOMYCIN 150 MG Q 6 HR
J.S.B. ♂, 18 MOS.
TEMP.
VOMITING WITH PAROXYSMS
VOMITED ALL FOOD
NUMBER OF PAROXYSMS
MILD
MODERATE
SEVERE
CULTURES (H. PERTUSSIS) W.B.C. X 1000
TERRAMYCIN 200 MG Q 6 HR
STOPPED DUE TO DIARRHEA & SEVERE VOMITING
SCARLATINIFORM RASH & ULCERATIVE STOMATITIS. CULTURES: HEM. STAPH. AUREUS (NEG. FOR BETA STREP.)
R.T. ♂, 2½ YR.
NO REACTION AFTER ORAL DOSE OF TERRAMYCIN
AUREOMYCIN 200 MG Q 6 HR
ALL MEDICATION DISCARDED
R.G. ♂, 2 YR.
CHLORAMPHENICOL 125 MG Q 6 HR
TERRAMYCIN 125 MG Q 6 HR
T.M. ♂, 8 MOS.

Fig. 3.—Clinical and bacteriological charts of four patients with unusual findings following antibiotic treatment for whooping cough.

It was necessary to omit medication because of toxic manifestations before the prescribed ten-day course was completed in only two patients of the 150 who were treated with any of the agents. One of these two patients received terramycin and his course is shown in the upper right panel of Fig. 3.

rash appeared and the patient developed severe diarrhea and vomiting. On the fifth day he developed an extensive ulcerative stomatitis and pharyngitis. Pharyngeal swabs throughout this period continued to yield coagulase positive, hemolytic *Staph. aureus*, essentially in pure culture. The mouth lesions prohibited oral feeding for several days, and despite maintenance of caloric intake by par-

enteral feeding, weight loss was marked. The whooping cough in this patient appeared to be progressing satisfactorily at first. The nasopharyngeal culture became negative for *H. pertussis* after forty-eight hours of treatment and remained so thereafter. Paroxysmal coughing had shown progressive decline, but then recurred after the terramycin was omitted. A test dose of terramycin given by mouth seven weeks later was not followed by any symptoms of drug sensitivity.

One patient who received aureomycin developed vomiting, pharyngitis, and a scarlatiniform rash on the ninth day of treatment and in this patient also the medication was promptly discontinued. Pharyngeal cultures in this case also showed coagulase positive hemolytic *Staph. aureus* essentially in pure culture.

The strains of staphylococci isolated in these two patients at the time of their scarlet fever were all resistant to 1,600 μg. per milliliter of penicillin, 800 μg. of terramycin and 200 μg. of aureomycin. They were only partially inhibited by chloramphenicol in concentrations ranging from 3 to 100 μg. per milliliter in one case and 12.5 to 100 μg. per milliliter in the other.

In the lower panels of Fig. 3 are shown the findings in two additional cases in which therapy failed either clinically or bacteriologically. The patient shown on the lower left represents the only one among those treated with any of the agents other than penicillin in whom *H. pertussis* persisted in the pharyngeal cultures during treatment. This patient had a very mild illness, but, as noted, he discarded nearly all of his medicine. In the lower panel on the right of Fig. 3, data are presented from a patient in whom chloramphenicol therapy resulted in a bacteriologic remission without appreciable clinical benefit during the treatment period. After the treatment was discontinued there occurred a marked increase in clinical symptoms associated with a bacteriologic relapse. The patient was then treated with terramycin and showed prompt clinical improvement and *H. pertussis* was again rapidly eliminated from the nasopharyngeal cultures.

Clinical Follow-Up.—It was possible to see and examine sixty-nine of the 150 patients from one to four months after discharge from the hospital; these included nineteen infants and fifty of the children over 1 year of age. A history was obtained at that time concerning any symptoms after returning home. Twelve of the nineteen infants did well at home, except for very slight coughing in five of them. The other seven infants, which included one who had been treated with aureomycin and two from each of the groups treated with other antibiotics, had moderate or severe coughing spells for one to two weeks at home, and these were accompanied by vomiting in three cases. Most of the children over 1 year of age also did well at home. There were six children among fifteen seen in the follow-up after penicillin therapy who had moderate or severe coughing, accompanied in each instance by vomiting. Among the thirty-five patients who were seen after treatment with any of the other antibiotics, ten continued to have moderate cough for a few days at home, and this was associated with some vomiting in five of them.

DISCUSSION

The analysis of the cases included in this study indicates that the pa-

tients in each of the four antibiotic treatment groups were quite comparable in almost all important respects at about the time when treatment was started. The results of treatment in these cases indicate that *H. pertussis* is eliminated quite promptly and with great regularity from the nasopharynx of patients with whooping cough who are treated with either aureomycin, chloramphenicol, or terramycin in the doses used. If the treatment with these agents is maintained for ten days, *H. pertussis* cannot be isolated from the pharyngeal cultures after the third or fourth day of treatment except in unusual circumstances. On the other hand, penicillin given by mouth in similar doses and supplemented at times with intramuscular doses appears to have no appreciable effect on the recoverability of *H. pertussis* from the nasopharynx of similar patients. The difference is quite striking and is of particular interest in view of the fact that on a weight basis, recently isolated strains of *H. pertussis* are not much less sensitive in vitro to penicillin than they are to the other three antibiotics.[4]

Clinically, the patients began to improve quite rapidly and steadily soon after treatment with either aureomycin, chloramphenicol, or terramycin was started, while the improvement in those who were treated with penicillin occurred much more gradually. In the infants under 1 year of age, the relatively greater improvement in toxicity, appetite, and general appearance of those treated with aureomycin, chloramphenicol, or terramycin was paralleled by the much more rapid decrease in the number and severity of paroxysms of coughing, cyanosis, and vomiting as compared with those who received penicillin. In the older children, on the other hand, this difference in the rate of decrease in the number of paroxysms of coughing was not nearly so striking although, in general, the improvement in general appearance, appetite, and interest in environment was similar to that observed in infants. It was felt that this discrepancy depended largely on the greater suggestibility of the older children in whom paroxysms of cough were much more readily precipitated by the coughing of other children who were in near-by beds in the same room.

The occurrence of exacerbations of cough after antibiotic therapy was ended in some patients, in spite of the fact that *H. pertussis* did not reappear in the nasopharyngeal cultures, is of some interest. This suggests, first, that the beneficial effects of these antibiotics on the whooping cough persists while the treatment is being continued and after the organisms have been markedly suppressed and apparently eliminated. It is also possible that the persistent effect may represent, in part, a result of the suppression of other respiratory pathogens.

A comparison of these results with those previously reported by Chang and associates[1] is of interest. In the earlier study, the patients treated with aureomycin were compared with similar ones to whom no antibiotic was given. In the latter, the frequency and severity of paroxysmal cough remained essentially unchanged for two to three weeks, while in those treated with aureomycin they declined rapidly and steadily, as in the present study. The patients treated with penicillin in this study, on the other hand, showed a steady, though gradual, decrease in the paroxysmal cough after treatment

was started. This was shown more clearly when curves were constructed for either the average daily number of paroxysms or the average daily "cough index" for the six infants in whom penicillin was either started after the first week in the hospital or was not given at all. When these curves were compared with the corresponding ones prepared for the remaining infants in whom penicillin was started soon after admission, it was seen that the former were flat for over two weeks and then began to decline, while the latter showed a slightly more rapid decline than is indicated for all the infants in the penicillin group as shown in Fig. 1. This suggests that penicillin, too, has a definite beneficial effect on the occurrence and severity of paroxysms of cough but that this effect is much less striking than that which accompanies treatment with either aureomycin, chloramphenicol, or terramycin. The effects of the three latter agents in whooping cough appear to be quite comparable in almost every important respect.

A large proportion of the infants had a history of previous immunization with pertussis antigens. When the severity and course of the illness among the immunized patients was compared with those of uninoculated patients, it appeared that the immunization had a moderating effect on the disease. Thus, of forty-seven children over 1 year of age and previously immunized, only six, or 13 per cent, were judged as having severe disease, while fourteen of the fifty-three unimmunized children in that age group, or 26 per cent, had a severe illness. The number of infants under 1 year of age who had been immunized prior to their illness was small and, in most of them, the course of immunization had not been completed. Nevertheless, even in this group, severe cases were half as frequent in the immunized as in the unimmunized infants. None of the three infants who had completed the prescribed course of immunization had a severe illness.

The preliminary results dealing with the antibody response in the present groups of cases suggest that the more rapid elimination of *H. pertussis* from the nasopharynx following treatment with aureomycin, chloramphenicol, or terramycin produces a delay and decrease in specific antibody production as compared with that observed in the penicillin-treated cases. However, the crude method used and the well-known difficulties with agglutination tests with *H. pertussis* indicate that these results should be interpreted with caution. A more detailed and controlled study of the immune response in pertussis is now in progress.

SUMMARY AND CONCLUSIONS

Penicillin, aureomycin, chloramphenicol, and terramycin were given in oral doses of 60 mg. per kilogram per day for ten days to 150 patients with whooping cough including fifty who were under 1 year of age.

Following the institution of treatment with aureomycin, chloramphenicol, or terramycin, *H. pertussis* was eliminated from nasopharyngeal cultures in three to four days and then could no longer be recovered, while this organism persisted for two weeks or longer in most of the penicillin-treated patients.

Aureomycin, chloramphenicol, and terramycin produced rapid improvement in the general condition in

almost every case while only a few patients showed significant or rapid improvement during treatment with penicillin.

In the patients treated with aureomycin, chloramphenicol, or terramycin, particularly in those under 1 year of age, the frequency and severity of the paroxysmal cough decreased more rapidly than in the penicillin-treated cases. In some patients, however, there was an exacerbation of cough after the treatment was stopped. There was suggestive evidence that penicillin had a slight salutory effect on the whooping cough.

The effects of aureomycin, chloramphenicol, and terramycin were quite similar in all respects.

Preliminary observations on the agglutinin response in some of these patients suggested that the suppression of *H. pertussis* by aureomycin, chloramphenicol, or terramycin may have delayed and reduced the antibody response.

REFERENCES

1. Chang, S-M., Wells, E. B., Place, E. H., and Finland, M.: Aureomycin Treatment of Pertussis, J. PEDIAT. **36**: 443, 1950.
2. Bradford, W. L., Day, E., and Berry, G. P.: Improvement of the Nasopharyngeal Swab Method of Diagnosis in Pertussis by the Use of Penicillin, Am. J. Pub. Health **36**: 468, 1946.
3. Verwey, W. F., Thiele, E. H., Sage, D. M., and Schuchardt, L. F.: A Simplified Liquid Culture Medium for the Growth of Hemophilus pertussis, J. Bact. **58**: 127, 1949.
4. Wells, E. B., Chang, S-M., Jackson, G. G., and Finland, M.: Antibiotic Spectrum of Hemophilus pertussis, J. PEDIAT. **36**: 752, 1950.

THE USE OF CAROB FLOUR (AROBON*) IN A CONTROLLED SERIES OF INFANT DIARRHEA

THOMAS R. PLOWRIGHT, M.D.**
FRESNO, CALIF.

THE San Joaquin Valley has long been known for its fertility and massive production of fruits, grapes, cotton, and other agricultural products. The planting, caretaking, and harvesting of these crops is accomplished in the large part by migrant workers who, as the name signifies, go from one crop to the next, living in tents, leantos, and even out in the open. The majority of these workers congregate in groups, and a large number of their camps are indeed lacking in sanitary conveniences. While the parents and older members of the family are out in the heat of the day toiling at their respective jobs, the younger members of the family are left to take care of themselves and eat and manage as best they can. The season of these migrant workers is from approximately the middle of April to the middle of December. During this period, the county hospitals of the Valley are flooded with cases of diarrhea in the younger age group, that is, up to 4 years of age, the majority of the patients being under 1 year of age. For the past few years the General Hospital of Fresno County has been confronted with this problem, admitting on the average of fifty cases of diarrhea and dehydration in infants per month. Needless to say, this puts a heavy load on the institution as well as on the taxpayers of the county, as it has been figured that the infant-hospital-day costs about seventeen dollars.

Nearly all of these patients with diarrhea have negative stool cultures and it is my belief that the contributing factors in the etiology of this type of diarrhea are: (a) poor eating habits, (b) inadequate diet, (c) excessive exposure to heat, culminating in dehydration, and (d) poor sanitary conditions in and around the labor camps. The majority of the infants enter the hospital with the chief complaint of vomiting and diarrhea of anywhere from two days to two weeks, with as many as fifteen to twenty watery stools per day. By the time the children reach the hospital they are severely dehydrated and most of them are in moderate to severe acidosis. The mode of treatment has been to give them either plasma or blood on admission, followed by electrolytes by all routes to correct

*Arobon is a commercial preparation manufactured by the Nestlé Company, Inc., and has the following composition according to the manufacturer:

Fat (ether extract)	0.5%
Protein (N × 5.7)	3.5%
Soluble carbohydrate (sucrose and reducing sugars)	49.0%
Other carbohydrate (hemicellulose and pectin)	22.0%
Starch	13.0%
Crude fiber	6.0%
Minerals (ash)	2.5%
Moisture	3.5%
Calories	250 per 100 Gm.

1 oz. by dry weight equals 75 calories
1 tablespoonful equals 19 calories

This material is obtained from the fruit of the carob tree, a leguminous plant which is native to the shores of the Mediterranean. The fruit is a bean-shaped pod which contains a sweet pulp, and which, as shown above, is rich in sugar and low in protein. When dried, it can be made into a powder which remains in a fine suspension when placed in water. The pulp is very rich in lignin, and it is believed that the mechanical effect of the preparation is based on this portion of its make-up.[1]

**Resident in Pediatrics, the General Hospital of Fresno County.

their acid and base imbalance and to restore their state of hydration, and then to put them on progressive fluids by mouth as soon as they can tolerate anything orally. Most of the antidiarrheal agents have been tried at one time or another without much effect, for these children continue to pass green watery stools even after they are in a state of normal hydration and electrolyte balance, some for as long as fifteen to twenty days.

After the report of Smith and Fischer,[1] it was decided to try and obtain some Arobon* and to compare its action with our standard method of treatment. The results of the trial with the Arobon is the subject of this report. Because of the excellent response to this substance, it was believed that a preliminary report of twenty cases should be published to enable those physicians treating diarrhea in infants to become acquainted with the material, as it is believed that this is the second report to be published in the United States, the first and only other article being the one of Smith and Fischer referred to above.

HISTORY

The use of the fruit of the carob tree as an antidiarrheal agent is not new. For years the Hindu population in and around Fresno, Calif., have been using this substance as a "home remedy" in the treatment of diarrhea. Its use as a food substance dates back to biblical times, when it is believed that the "seeds and sugary pulp" of the carob tree were the "locusts and wild honey" which St. John the Baptist found in the wilderness.[2] Hence the name by which the tree is known in some parts of the world—the Saint John Tree. Also it is thought that in the story of the prodigal son, the husks that are referred to were in reality the pods of the carob tree.[2]

Cultivation of the tree began in historic times and was diffused by the Greeks in Italy and Greece and was carried by the Arabs as far west as Spain and Morocco. In these countries the fruit has been used for forage, as food by the poorer people, and used for the manufacture of syrups and various fermented drinks. It was the main sustenance of Wellington's troops during the Peninsular campaign. It has been said that an acre of carob trees on arid soil yields much greater quantity of food matter than an equal area of alfalfa. These trees were introduced to the United States in 1854 from Spain.[3]

During the Spanish Civil War it was noticed by Ramos[4] of Barcelona, Spain, that the children of the poorer classes in Barcelona who ate the fruit of the carob tree had fewer diarrheal disturbances than did those of the wealthier classes. Using this as his criteria, he made a concoction using the dried pulp of the roasted carob mixed with starch for the treatment of diarrhea. The product was manufactured abroad under the name of Arobon. Since the time of this original study of the material, numerous reports have been published in the foreign literature.[5-8] The material is now available for general use in the United States.

METHOD OF STUDY

Our subjects consisted of forty infants between the age of 1 week and 1 year who entered the hospital with the diagnosis of diarrhea or diarrhea and dehydration. Every other one of these patients was put in the control

*See footnote, p. 16.

TABLE I. CONTROL GROUP

NAME	AGE IN MONTHS	DAYS OF ILLNESS	NO. AND CHARACTER OF STOOLS PER DAY PRIOR TO ADMISSION	CO_2 COMBINING POWER ON ADMISSION %	DEGREE OF DEHYDRATION	TYPE OF FLUID REPLACEMENT*	RESULTS OF STOOL CULTURE	WEIGHT ON ADMISSION	WEIGHT ON DISCHARGE	NO. OF HOURS ON FORMULA PRIOR TO FIRST FORMED STOOL	NO. OF HOURS BEFORE CURE	NO. OF DAYS IN HOSPITAL
J. V.	1½	7	12-15 green liquid	28	++++	SC, IP, IV	Negative	6 lb. 13 oz.	7 lb. 12 oz.	138	264	11
S. G.	3	2	7-8 green-yellow	48	+++	SC, IP, IV	Negative	8 lb. 11 oz.	9 lb. 12 oz.	100	240	10
A. M.	5	2	15-20 green liquid	26	++++	SC, IP, IV	Negative	12 lb. 0 oz.	12 lb. 7 oz.	134	240	10
C. R.	3	2	10 watery green	32	++	SC, IP	Negative	7 lb. 8 oz.	8 lb. 0 oz.	154	288	12
G. F.	9	3	5-6 watery with blood	27	++	SC, IP	Negative	12 lb. 10 oz.	13 lb. 15 oz.	372	624	26
S. W.	1½	3	8-10 watery green	38	+++	SC, IP, IV	Negative	6 lb. 12 oz.	8 lb. 2 oz.	144	240	10
F. R.	1½	4	6-8 watery green	40	++	SC	Negative	7 lb. 1 oz.	8 lb. 4 oz.	92	192	8
J. M.	3	8	10-12 green liquid	18	++++	SC, IP, IV	*Pr. morganii*	8 lb. 11 oz.	8 lb. 14 oz.	220	434	20
P. D.	9	3	6-10 yellow watery	34	++	SC, IP	Negative	14 lb. 12 oz.	16 lb. 8 oz.	180	394	16
O. R.	8	2	12-14 watery with blood	38	++	SC, IP	Negative	15 lb. 8 oz.	16 lb. 7 oz.	146	288	12
R. R.	6	6	7-12 green liquid	30	+++	SC, IP	Negative	12 lb. 4 oz.	13 lb. 6 oz.	212	388	17
B. S.	2	1	8-10 yellow watery	50	+	SC	Negative	8 lb. 1 oz.	8 lb. 8 oz.	38	192	8
S. M.	1	4	6-10 watery with blood	42	++	SC, IP	Negative	7 lb. 8 oz.	7 lb. 12 oz	170	312	13
E. D.	8	7	Unknown	18	++++	SC, IP, IV	Negative	14 lb. 6 oz.	15 lb. 8 oz.	312	574	24
O. J.	12	2	7-9 yellow liquid	54	++	SC	Negative	18 lb. 7 oz.	22 lb. 0 oz.	190	394	16
R. G.	6	3	14 green watery	42	+++	SC, IP	Negative	13 lb. 6 oz.	14 lb. 7 oz.	162	384	14
F. M.	4	3	12-14 green watery	34	+++	SC, IP	Negative	9 lb. 7 oz.	9 lb. 14 oz.	182	312	13
M. G.	2	2	6-8 yellow liquid	46	++	SC	Negative	8 lb. 2 oz.	8 lb. 15 oz.	168	288	12
I. L.	3	2	6-8 watery with blood	48	+	SC	Negative	11 lb. 2 oz.	12 lb. 9 oz.	126	240	10
F. L.	5	2	7-10 green liquid	40	+++	SC	Negative	13 lb. 6 oz.	14 lb. 14 oz.	246	504	21
									Total	3,486	6,792	283
									Average	174.3	339.6	14.15

*SC = Subcutaneous.
IP = Intraperitoneal.
IV = Intravenous.

TABLE II. AROBON GROUP

NAME	AGE IN MONTHS	DAYS OF ILLNESS	NO. AND CHARACTER OF STOOLS PER DAY PRIOR TO ADMISSION	CO_2 COMBINING POWER ON ADMISSION %	DEGREE OF DEHYDRATION	TYPE OF FLUID REPLACEMENT*	RESULTS OF STOOL CULTURE	WEIGHT ON ADMISSION	WEIGHT ON DISCHARGE	NO. OF HOURS ON AROBON PRIOR TO FIRST FORMED STOOL	NO. OF HOURS ON AROBON BEFORE CURE	NO. OF DAYS IN HOSPITAL
F. N.	7	2	10 green liquid	18	++	SC, IP	Negative	11 lb. 3 oz.	15 lb. 1 oz.	27	99	8
R. T.	9	6	8-10 green watery	30	+++	SC	Negative	13 lb. 2 oz.	15 lb. 4 oz.	22	94	9
D. O.	3	2	7-12 yellow watery	40	+++	SC	Negative	11 lb. 10 oz.	12 lb. 4 oz.	26	98	8
M. P.	7	3	6-8 yellow-green	50	++	SC, IP	Negative	11 lb. 10 oz.	13 lb. 2 oz.	144	216	10
S. J.	3	4	18-20 green watery	28	++++	SC, IP, IV	Negative	7 lb. 11 oz.	8 lb. 15 oz.	32	104	6
J. N.	6	3	4 yellow-green	46	++	SC	Negative	14 lb. 11 oz.	17 lb. 0 oz.	42	114	7
M. M.	2	7	5-7 yellow-green	42	++	SC, IP, IV	Negative	6 lb. 9 oz.	7 lb. 6 oz.	16	88	6
R. L.	4	2	Unknown	16	++++	SC, IP	Negative	5 lb. 4 oz.	6 lb. 14 oz.	78	150	10
B. O.	3	1	14 green watery	30	+++	SC	Negative	7 lb. 4 oz.	9 lb. 8 oz.	120	192	10
M. W.	4	3	6-8 watery with blood	51	++	SC, IP	Negative	9 lb. 1 oz.	10 lb. 14 oz.	56	128	8
D. O.	2	7	8-10 green liquid	38	+++	SC, IP, IV	*Pr. morganii*	8 lb. 10 oz.	9 lb. 2 oz.	32	104	8
M. D.	¾	6	14-16 watery green	34	+++	SC, IP	Negative	6 lb. 13 oz.	7 lb. 9 oz.	28	100	10
J. B.	5	4	5-7 green with blood	36	++	SC, IP	Negative	13 lb. 6 oz.	14 lb. 8 oz.	26	98	7
N. R.	8	5	6-8 green watery	38	+++	SC, IP	Negative	14 lb. 7 oz.	16 lb. 3 oz.	34	106	6
B. L.	12	2	14-20 watery	18	++++	SC, IP, IV	Negative	18 lb. 6 oz.	21 lb. 2 oz.	76	148	9
S. M.	6	3	5-10 green watery	28	+++	SC, IP, IV	Negative	11 lb. 14 oz.	15 lb. 12 oz.	84	156	9
B. D.	1	7	8-12 loose green	31	++	SC, IP	Negative	10 lb. 15 oz.	12 lb. 13 oz.	16	88	5
L. R.	10	1	4-5 watery yellow	46	+	SC	Negative	14 lb. 6 oz.	16 lb. 4 oz.	22	94	7
M. S.	3	2	6-10 green liquid	40	++	SC	Negative	8 lb. 11 oz.	9 lb. 14 oz.	36	108	6
M. N.	1	3	7-12 watery with blood	48	++	SC, IP	Negative	6 lb. 3 oz.	7 lb. 8 oz.	44	116	8
									Total	959	2,401	157
									Average	47.95	120.05	7.85

*SC = Subcutaneous.
IP = Intraperitoneal.
IV = Intravenous.

group, and the others in the Arobon group. All patients were given 300,000 units of crystalline penicillin on admission and every twelve hours while under observation, 250 mg. of dihydrostreptomycin every six hours (alternating between oral and intramuscular route); each had a carbon dioxide combining power determination on admission; stool cultures for parasites, ova, and bacteria were obtained from each patient on three successive days; and the usual admitting laboratory work, such as complete blood count, urinalysis, and serology was done. Fluid and electrolyte replacement was instigated immediately and the type of fluid and route of administration were determined for each patient depending on the severity of the dehydration and amount of acidosis.

In order to determine the best practical means of treating the control group, the diarrhea cases for the past several years were reviewed. Along with these cases and our own experience in treating this type of diarrhea, it was decided that after a short starvation period this group was to be put on a progressive fluid regime, starting out with Ringer's-lactate by mouth. As the infant's tolerance to oral feeding increased the formula was changed from the Ringer's-lactate to half strength -boiled skimmed milk. This formula was kept up until the stools began to form; then the strength of the milk formula was gradually increased until the child was on the "going home formula." During the early phase of this regime the daily fluid requirements were met with a combination of oral and parenteral administration.

The Arobon group were to be treated identically, except that when the starvation period was over, a 5 per cent solution of Arobon was given by mouth. As much as could be tolerated by the infant was given every four hours and the child was offered a solution of 5 per cent glucose in water between feedings. As soon as a true formed stool was passed, the 5 per cent Arobon solution was diluted half and half with the infant's "going home formula." The patient was kept on the latter formula for the next twenty-four hours and then put on the "going home formula" and watched in the hospital for twenty-four to forty-eight hours.

RESULTS

From Tables I and II it can be seen that the type of diarrhea being treated is not bacterial in origin as nearly all of the stool cultures are negative; that the severity of the diarrhea was equally distributed among both groups; the average number of hours for the first formed stools to be obtained in the control group was 174.3 as compared to 47.95 in the Arobon group; the average number of hospital days required for treatment of the control group was 14.15 as compared to 7.85 for the Arobon group; the average number of hours before cure in the control group was 339.6 while the Arobon group was 120.05.

DISCUSSION

All of the patients in this series were followed in out-patient clinic for a period of two weeks and were seen at weekly intervals. During this two-week period of follow-up there were no relapses in either group. Two of the patients in the Arobon group complained of "constipation" for several days following discharge from the hospital. This is believed to be due to not starting the dilution of the 5 per cent Arobon with the "going home for-

mula" quite soon enough. There were no adverse side effects which could be attributed to the use of the Arobon.

We have used Arobon on a considerable number of diarrheal patients who were not considered sick enough to be admitted to the hospital and were treated in the out-patient department. Although we have kept no accurate results on these patients it is interesting to note that all those who were treated in this manner began having formed stools and their diarrhea cleared in a maximum of forty-eight hours. The regime used on the out-patients was identical with that used on the in-patients so far as the administration of Arobon was concerned.

Another point of interest in regard to the Arobon group was that not one of the patients refused to take the formula, but, on the contrary, all took it wholeheartedly.

CONCLUSIONS

Our experience with Arobon in the treatment of infant diarrheal disturbances has been encouraging and it appears to assist in controlling the diarrhea in a period of from sixteen to 144 hours. No adverse side effects to the product were elicited. In our limited experience in the use of this material it would seem that it should be of great value in the treatment of mild to moderate cases of diarrhea on an out-patient basis. Further studies and comparison with other antidiarrheal agents is undoubtedly indicated.

SUMMARY

Forty cases of infant diarrhea were studied. These cases were equally divided into two groups, one group being placed as a control and treated under the standard regime for diarrheal care at this hospital while the other group was treated with a new product (Arobon). Those treated with the Arobon began having formed stools in about one-half the time it took the control group. Also the number of hospital days was practically cut in half for the Arobon group. This product did not produce adverse side effects in our experience.

The author wishes to express his thanks to Walter A. Rohlfing, Jr., M.D., Director, General Hospital of Fresno County, for his untiring efforts to make all the necessary equipment and personnel available for this study. Also to Dean Hyde, M.D. and Edward Defoe, M.D., from the Department of Pediatrics, General Hospital of Fresno County, for their help and guidance in the treatment of the acidosis and dehydration of the patients making up this series.

REFERENCES

1. Smith, Alan E., and Fischer, Carl C.: The Use of Carob Flour in the Treatment of Diarrhea in Infants and Children, J. PEDIAT. 35: 422, 1949.
2. Yearbook of Agriculture, p. 823, 1949.
3. Standard Cyclopedia of Horticulture, vol. II, p. 717.
4. Ramos, R., and Rozalen, M.: Un Nuevo Alimento-Medicamento: La Harina de Algarroba, Rev. espan. farm. y terap. 21: 1339, 1941.
5. Megevand, J., and Riederer, V. de: Une Nouvelle Therapeutique pour les Troubles Digestifs Graves des Nourissons (Dyspex), Rev. méd. de la Suisse Rom. 61: 330, 1941.
6. Neyroud, M.: Carob Flour, a New Antidiarrheic Medicine, Ann. Paediat. 166: 113, 1946.
7. Martin du Pan, R.: The Antidyspeptic Properties of Ceratonia Siliqua, Ann. Paediat. 165: 205, 1945; The Carob Bean, Its Antidyspeptic Properties, Schweiz. med. Wchnschr. 75: 763, 1945.
8. Nicod, M.: The Use of Carob Flour in the Treatment of Infantile Gastro-Intestinal Disorders, Praxis 36: 105, 1947.

THE LOCAL EFFECT OF CORTISONE ON THE TUBERCULIN REACTION

HERMANN VOLLMER, M.D.
NEW YORK, N. Y.

INTRODUCTION

STOERK[1] demonstrated a suppression of the tuberculin reaction in guinea pigs sensitized with heat-killed tubercle bacilli when cortisone was administered prior to the injection of old tuberculin.

Subsequently, Long and Favour[2] demonstrated a similar phenomenon in man. In thirty-four patients, the skin reactions to purified protein derivative were decreased or obliterated during treatment with cortisone or ACTH. The degree of obliteration was affected by the hormone dosage and the duration of treatment. Seven to twenty-eight days after cessation of treatment, a return of the sensitivity reactions occurred in each patient tested.

These observations can be explained in two ways. Systemic treatment with cortisone or ACTH may influence skin reactions of the tuberculin type either directly by producing a certain cortisone concentration in the epidermis, or indirectly through mediation of other mechanisms affected by these hormones.

The following experiments, in which small amounts of cortisone mixed with tuberculin were injected intracutaneously in sensitive individuals, clarify the mode of action. They also permit close observation of the direct cortisone effects on easily accessible tissues.

METHOD AND MATERIALS

Old tuberculin (New York City Department of Health) in dilution of 1:10,000 was used for these experiments. An amount of 0.05 c.c. of this dilution was mixed in a tuberculin syringe with an equal amount of isotonic sodium chloride solution and injected intracutaneously on the volar surface of the left forearm. On a symmetrical site of the right arm of the same individual, 0.05 c.c. of the same tuberculin dilution mixed in the syringe with 0.05 c.c. of commercially available saline suspension of crystalline cortisone* (= 1.25 mg. cortisone acetate) was injected intracutaneously. The reactions were read every twenty-four hours, for five days. Erythema as well as induration were measured in their smallest and largest diameters; the means of both measurements in millimeters were used in the charts to indicate the degree of the skin reactions.

In a few instances, ACTH solution (0.5 mg. ACTH in 0.05 c.c. of saline solution) was used instead of cortisone for otherwise identical experiments.

Controls with cortisone were carried out by intracutaneous injection of 0.05 c.c. of the same cortisone suspension mixed in the syringe with an equal amount of saline solution.

*Cortone, Merck & Co., Inc.

Schick tests were done in a similar way using diphtheria toxin of the New York City Department of Health. On the volar surface of the left forearm, a mixture of 0.05 c.c. of diphtheria toxin and 0.05 c.c. of saline solution was injected intracutaneously, and in a corresponding area of the right arm, a mixture of 0.05 c.c. of diphtheria toxin and 0.05 c.c. of cortisone suspension. The reactions were read every twenty-four hours, for five to seven days.

On several individuals, local differential white blood counts were made simultaneously in the area of the reactions, both to tuberculin alone and to tuberculin plus cortisone. Forty-eight hours after the injection of these substances, the skin was punctured superficially at the center of the skin reactions and a blood smear made without the use of pressure to accelerate bleeding.

In one volunteer, skin biopsies were taken from both skin reactions forty-eight hours after intracutaneous injection of tuberculin and tuberculin plus cortisone, respectively. Punch biopsy was made as near the center of the reaction as possible without including the needle tract of the test injection. The specimens were processed for histological examination within one hour after the biopsies.

All experiments were done in adult volunteers who were physicians, most of them pediatricians who assured an excellent cooperation. They measured and tabulated daily the skin reactions, and their figures were accepted as the results of impartial observation. I saw the skin reactions at least once during their course to check the data given by the volunteers.

RESULTS

In each of nine cases the tuberculin reactions were decreased by local cortisone, in the majority of them strikingly. In all but one case the reactions to tuberculin plus cortisone, according to accepted standards, would have been interpreted as negative at the forty-eight-hour reading, in contrast to the corresponding positive reactions to tuberculin without cortisone. Table I contains the detailed data; Fig. 1 illustrates the means of both reactions in nine individuals over a period of five days. The means of the differences between both reactions in the individual cases are charted in Fig. 2. This figure demonstrates that the induration is more suppressed by cortisone than is the erythema.

In evaluating this difference it must be considered that cortisone itself elicits a skin reaction. Table II shows the effects of intracutaneously injected cortisone in eleven individuals; the mean of these reactions is illustrated in Fig. 3. If one compares this curve with the curve of the skin reactions to tuberculin plus cortisone (Fig. 1), it is evident that a part but not all of the latter may be ascribed to the traumatic effect of the intradermally injected cortisone crystals. A comparison of Figs. 1 and 3 further suggests that the initial erythema appearing twenty-four hours after intracutaneous injection of tuberculin plus cortisone is due mainly to the traumatic effect of cortisone.

In seven of nine cases, marked itching occurred at the site of the skin reaction to tuberculin but was absent at that of the reaction to tuberculin plus cortisone. This may only mean that the degree of itching depends on

TABLE I

CASE	SKIN REACTIONS TO 0.005 MG. OLD TUBERCULIN										SKIN REACTIONS TO 0.005 MG. OLD TUBERCULIN + 1.25 MG. CORTISONE									
	24 HR.		48 HR.		72 HR.		96 HR.		120 HR.		24 HR.		48 HR.		72 HR.		96 HR.		120 HR.	
	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E
1	9	19	11	20	5	7.5	0	0	0	0	5	6.5	2.5	5	0	0	0	0	0	0
2	10	12.5	12	20	12	19.5	12	16	8	12	12.5	26.5	5	10	2	10	2	12	0	12
3	5	25	15	30	15	25	10	15	10	15	0	20	0	25	0	10	0	5	0	0
4	7.5	15	10	15	7.5	15	10	10	10	10	2	25	2	20	5	10	5	5	5	5
5			13.5	13.5									2	3						
6	15	18	15	31.5	12.5	20	10	13			7	27.5	4	4	0	3	0	3		
7	15	20	15	15	15	10	15	10	15	10	10	15	10	15	10	20	3	20	3	20
8	5	22.5	5*	5	6	7					2.5	20	7	7	0	0				
9	3	11	4*	18	biopsy						0	3	0	6	biopsy					
Sum	69.5	143	100.5	168	73	104	57	64	43	47	39	143.5	32.5	95	17	53	10	45	8	37
Mean	8.7	17.9	11.2	18.7	10.4	15	9.5	10.7	8.6	9.4	4.9	17.9	3.6	10.6	2.4	7.6	1.7	7.5	1.6	7.4

*Figures as reported by volunteer, seen by me at forty-eight hours, who felt that the degree of induration was greatly underrated and that this was unquestionably a positive reaction.

I = Millimeters of induration.

E = Millimeters of erythema.

the intensity of the skin reaction to bacterial antigen; it may also indicate a specific effect of cortisone.

It may be noteworthy that in three cases the skin reaction to tuberculin plus cortisone flared up and started to itch after the fifth day. A plausible explanation for this phenomenon is that tuberculin lay dormant in the skin and the skin reaction was temporarily suppressed until the intracutaneous cortisone deposit was completely absorbed and no longer effective.

Local blood counts were done at the site of both reactions of five individuals. In three (Cases 6, 4, and 3, Table III), which were examined after forty-eight hours, there was a relative decrease of the number of lymphocytes at the reaction to tuberculin plus cortisone. The number of eosinophiles did not show any significant difference. In a fourth case (Table III, Case 2), local blood counts were done seven days after the injection of the test substances; there was no significant difference between the two sides. In a fifth case, not shown in Table III, local blood counts were taken following punch biopsies. The bleeding in this case took place in the subcutis; both blood counts were equal. These findings suggest that cortisone has a local effect on lymphocytes.

As was to be expected, ACTH used locally like cortisone in the previous experiments failed to alter the tuberculin reaction in three individuals.

The suppression of the tuberculin reaction by cortisone can be explained in different ways. Cortisone may inter-

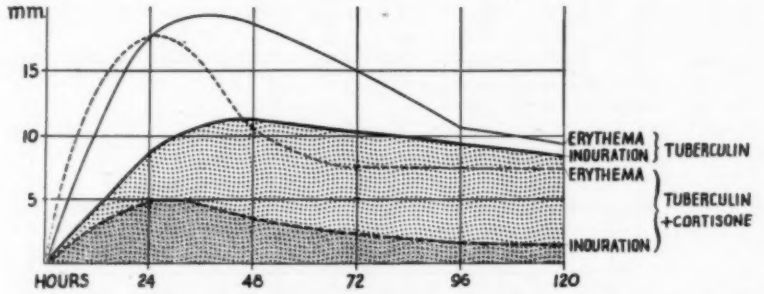

Fig. 1.—Means of skin reactions of nine individuals to 0.005 mg. old tuberculin and to 0.005 mg. old tuberculin plus 1.25 mg. cortisone, respectively.

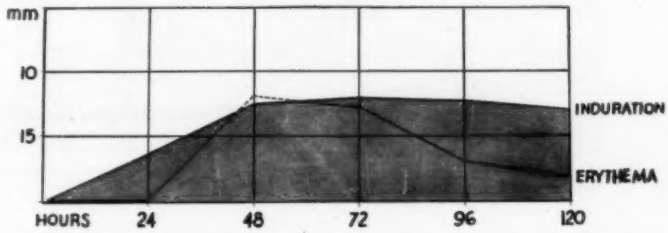

Fig. 2.—Means of the differences between both skin reactions in the individual cases (derived from Table I).

TABLE II

	SKIN REACTIONS TO 1.25 MG. CORTISONE									
	24 HR.		48 HR.		72 HR.		96 HR.		120 HR.	
CASE	I	E	I	E	I	E	I	E	I	E
1	2	20	1	7.5	0	0	0	0	0	0
2	2	5	0	1.5	0	0	0	0	0	0
3	0	5	0	0						
4	3.5	18.5	6.5	27.5	4	0	4	0	4	0
5	2.5	5	2	4	2	2	2	2	2	2
6	2	5	0	0	0	0	0	0	0	0
7	7	19	2	2	0	0	0	0	0	0
8	3	20	3	16	0	0	0	0	0	0
9	7	20	0	0	0	0	0	0	0	0
10	6	25	0	0	0	0	0	0	0	0
11	5	30	5	30	5	0	0	0	0	0
Mean	3.6	15.7	1.8	8.0	1.1	0.2	0.5	0.2	0.5	0.2

I = Millimeters of induration.
E = Millimeters of erythema.

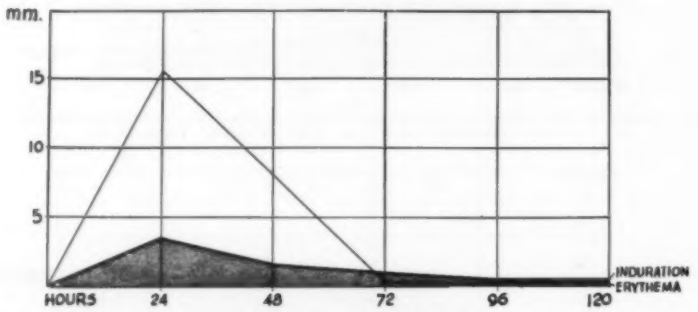

Fig. 3.—Means of the skin reactions to intracutaneously injected cortisone (1.25 mg.) in eleven individuals.

TABLE III. LOCAL BLOOD COUNTS

	OLD TUBERCULIN				OLD TUBERCULIN + CORTISONE			
CASE	CELLS P	L	M	E	P	L	M	E
6	52	46	2	0	68	30	1	1
4	42	57	1	0	53	41	6	0
2	55	37	7	1	58	36	3	3
3	63	36	0	1	73	24	2	1
Mean	53	44	2.5	0.5	63	32.75	3	1.25

P = Polymorphonuclear leucocytes.
L = Lymphocytes.
M = Monocytes.
E = Eosinophiles.

fere with the antigen-antibody reaction, it may decrease tissue response in general, both of these effects may play a role, or other unknown mechanisms may be operating. We thought that analogous experiments with the Schick test might throw light on the mode of action.

As shown in Table IV and Fig. 4, the Schick test too was altered by local cortisone. In five cases,* induration as well as erythema was decreased by general. As soon as cortisone is absorbed, the diphtheria toxin lying dormant in the skin may elicit a "rebound" reaction.

One objection may be raised against this interpretation. Diphtheria toxin is sensitive to acids,[3] and saline suspension of cortisone has a pH of 6. One could argue that the potency of diphtheria toxin is impaired by the acidity of cortisone, and that as a result of this the skin reaction is

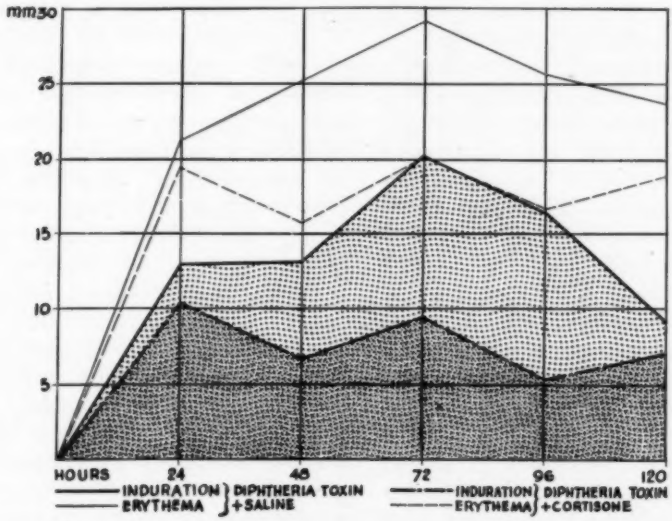

Fig. 4.—Means of skin reactions to 0.05 c.c. diphtheria toxin and to 0.05 c.c. diphtheria toxin plus 1.25 mg. cortisone, respectively.

cortisone. In one case, the reaction to diphtheria toxin plus cortisone flared up after the fifth day and exceeded the reaction to diphtheria toxin alone. Since no antigen-antibody reaction is involved in the Schick reaction, our observations seem to indicate that cortisone influences tissue reactivity in diminished. This impairment, however, is reversible.[3] It is to be anticipated that buffers of the extracellular fluid will neutralize the acid valences of cortisone suspension. The observed "rebound" reaction proves directly the persistence of potent diphtheria toxin in the tissues.

Therefore, cortisone actually seems to suppress the Schick reaction by affecting the reactivity of the tissues.

*Since we found only this limited number of Schick-positive individuals, Dr. Hans Mautner, Wrentham State School, Wrentham, Mass., assisted with identical experiments in fifteen children. His observations were similar to ours.

TABLE IV

CASE	SKIN REACTIONS TO DIPHTHERIA TOXIN										SKIN REACTIONS TO DIPHTHERIA TOXIN + CORTISONE									
	24 HR.		48 HR.		72 HR.		96 HR.		120 HR.		24 HR.		48 HR.		72 HR.		96 HR.		120 HR.	
	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E
1	3	16	3	21	5	23	5	18	2.5	13	6	24	9	0	7	0	2	0	1	0
2	5	10	5	10	10	10	5	5	2.5	2.5	3	5	3	5	3	3	3	3	3	3
3	0	0	0	12.5	19	22.5	20	22.5	20	21.5	3	13.5	0	16	0	27.5	0	20	0	20
4	35	35	37.5	40	40	40	40	40	21	42.5	30	30	10	15	20	25	20	20	32	32
5	22	45	20	42	27	50	13	43	0	40	10	25	12	43	18	45	3	40	0	40
Mean	13	21.2	13.1	25.1	20.2	29.1	16.6	25.7	9.2	23.9	10.4	19.5	6.8	15.8	9.6	20.1	5.6	16.6	7.2	19

I = Millimeters of induration.
E = Millimeters of erythema.

Whether the suppression of the tuberculin reaction is merely due to the same effect or to an additional interference with the antigen-antibody reaction remains undetermined.

HISTOLOGY

Skin biopsies were taken from one volunteer forty-eight hours after the intradermal injections of tuberculin and of tuberculin plus cortisone, respectively. The histological examinations were carried out by Dr. Paul Klemperer, Mount Sinai Hospital, New York. His report follows:

a. Tuberculin reaction: The epidermis shows moderate intercellular edema with a few polymorphonuclear leucocytes and occasional mononuclear wandering cells found between the epithelial cells. The papillary body shows edema, very slight dilatation of the capillaries, and moderate infiltration with lymphocytes and mononuclear wandering cells. The dermis shows conspicuous infiltration of cells between the collagen bundles, which is most striking around the ramifications of the vessels. The infiltrating cells are lymphocytes, histiocytes, and also polymorphonuclear leucocytes. Erythrocytes are also seen outside the vessels. The same cell infiltration in a slightly diminished degree extends into the subcutaneous fat tissue to the border of the excision.

b. Skin reaction to tuberculin plus cortisone: The epidermis shows minimal intercellular edema with only an occasional mononuclear wandering cell between the epithelial cells. The papillary body shows moderate perivascular infiltration with lymphocytes, histiocytes, and occasional polymorphonuclear leucocytes. A similar cell infiltration is seen around a hair follicle. Two areas in the middle and deep corium show the accumulation of a fibrillar material by which the collagen bundles are spread apart. Within these areas and in the adjacent corium there is a conspicuous infiltration mainly of polymorphonuclear leucocytes and fewer mononuclear wandering cells and a few lymphocytes. Fibroblasts with distorted nuclei are seen between the separated collagen fibers. The same cell infiltration extends into the subcutaneous fat tissue toward the depth of the excised skin.

c. Histological differences between both reactions: A comparison of the microscopic features of the two skin fragments indicates a difference in the intensity of the inflammatory reaction as well as in the quality of the inflammatory cell response. In the tuberculin reaction there is edema of the papillary body which is absent in the skin reaction to tuberculin plus cortisone. The perivascular cell infiltration of the upper corium is striking in the tuberculin reaction while it is moderate in the reaction to tuberculin plus cortisone and possibly not related to tuberculin. This is suggested by the presence of a moderate inflammation around a hair follicle. It is further suggested by the fact that the inflammation in this specimen is most severe in the immediate vicinity of the foreign material. The difference in the quality of the cell reaction is quite striking inasmuch as in the reaction to tuberculin plus cortisone polymorphonuclear leucocytes predominate while in the tuberculin reaction lymphocytes prevail.

DISCUSSION

It appears that systemic treatment with cortisone and ACTH depresses

the tuberculin reaction by producing a certain cortisone concentration in the epidermis and not through mediation of other mechanisms affected by these hormones. Our experiments indicate that it is cortisone and not ACTH which alters these skin reactions, and that cortisone acts locally.

Contradictory reports[2, 4, 5] of the capacity of ACTH and cortisone to alter positive skin tests, as well as the observations that skin reactions were suppressed in different degrees[2] or suppressed in one but not the other individual,[4] may be explained by different cortisone concentrations obtained in the epidermis by systemic treatment with cortisone or ACTH. The epidermal cortisone concentration may depend on the hormone dosage as well as the duration of treatment.

Cortisone seems to be able to suppress not only the tuberculin reaction but also skin reactions to other bacterial antigens,[2] to pollens and other extrinsic antigens,[4] and to diphtheria toxin. The fact that cortisone affects in a similar way skin reactions to substances of such different nature suggests that local cortisone decreases tissue reactivity in general. Whether, in the case of the tuberculin reaction, cortisone has an additional influence on the antigen-antibody reaction could not be determined. Such an influence might be suggested by the relative decrease of lymphocytes at the reaction to tuberculin plus cortisone which we observed in local blood counts and which were confirmed by independent histological examinations. Lymphocytes are thought to be operative in many immunological processes, among others in the formation of antibodies against tuberculoproteins.[2, 6-8] Our observations, however, cannot be regarded as incontestable proof that local cortisone interferes with the antigen-antibody reaction.

The skin reactions which occurred after intracutaneous injection of tuberculin plus cortisone probably represented to a greater extent traumatic reactions to cortisone. This conclusion, based on our clinical observations, was supported by independent histological findings. Klemperer wrote: "... it is not unreasonable to conclude that the inflammation in the cortisone experiments is due to the injection of the foreign material. It lacks the qualitative features of the tuberculin reaction."

The "rebound" reactions observed in several of the volunteers are noteworthy. They find an interesting clinical analogy in "rebound effects" recently described by Ragan[9] in three cases of rheumatoid arthritis following hormone withdrawal. In these cases, the arthritis became more severe after hormone treatment than it had been prior to this therapy.

The observation that locally applied cortisone suppresses inflammatory skin reactions as well as itching and possibly antigen-antibody reactions invited further investigation about the therapeutic value of topical cortisone. If it were possible to avoid larger systemic doses and to apply cortisone to the skin in such a way that small quantities are absorbed, therapeutic effects in skin diseases might be accomplished while systemic side effects are avoided. Preliminary therapeutic trials with cortisone ointment in five patients with eczema were promising. This is the subject of further investigation.

It occurred to us that cortisone as well as measles suppresses the tuberculin reaction, that cortisone as well as

measles improves many cases of nephrosis. Both cortisone and measles have other actions in common: they improve eczema and asthma; they decrease the number of circulating lymphyocytes and eosinophiles; they reduce lymph nodes in Hodgkin's disease and leucemia; and they retard wound healing. It might well be that the eruption of measles acts as a stress and increases cortisone excretion and that the serum of measles patients has therapeutic effects in the group of diseases which are benefited by cortisone and ACTH.

SUMMARY AND CONCLUSIONS

1. The local effect of cortisone has been studied by injecting intracutaneously 1.25 mg. of cortisone acetate in suspension, mixed with 0.005 mg. of old tuberculin, in nine sensitive volunteers.

2. The tuberculin reactions were diminished by cortisone in all cases. The induration was more affected than the erythema.

3. Local ACTH failed to alter the tuberculin reaction.

4. Cortisone itself elicited a traumatic skin reaction with a wide initial erythema. This reaction usually disappeared on the second day.

5. The skin reactions to tuberculin plus cortisone, mainly their initial erythema, were in part ascribed to the traumatic skin reaction caused by cortisone.

6. Local differential white blood counts examined after forty-eight hours showed a relative decrease of lymphocytes at the reaction to tuberculin plus cortisone as compared with the reaction to tuberculin alone.

7. In seven of nine cases, marked itching occurred at the skin reaction to tuberculin but was absent at the reaction to tuberculin plus cortisone.

8. In three cases, the skin reaction to tuberculin plus cortisone flared up after the fifth day. These "rebound" reactions seem to indicate that tuberclin lay dormant in the skin while cortisone temporarily suppressed the skin reaction.

9. Skin biopsies taken after forty-eight hours showed a striking difference in the degree as well as the quality of inflammatory reaction to tuberculin and to tuberculin plus cortisone, respectively. In the former, lymphocytes predominated; in the latter, polymorphonuclear leucocytes. The reaction to tuberculin plus cortisone lacked the qualitative features of the tuberculin reaction and seemed to be caused by the injection of cortisone suspension rather than by tuberculin.

10. Local cortisone decreased the skin reactions to diphtheria toxin in five individuals. One of them showed a "rebound" reaction after the fifth day.

11. It is concluded that local cortisone decreases tissue response in general. Whether an additional interference with the antigen-antibody reaction is responsible for the suppression of the tuberculin reaction by cortisone remains to be determined.

The cooperation of staff members of Babies Hospital and Vanderbilt Clinic, particularly of Dr. Conrad M. Riley, is gratefully acknowledged. I wish to thank Dr. Rustin McIntosh for his suggestions in editing the manuscript.

REFERENCES

1. Stoerk, H. C.: Inhibition of Tuberculin Reaction by Cortisone in Vaccinated Guinea Pigs, Federation Proc. **9**: 345, 1950.
2. Long, J. B., and Favour, C. B.: The Ability of ACTH and Cortisone to Alter Delayed Type Bacterial Hypersensitivity, Bull. Johns Hopkins Hosp. **87**: 186, 1950.

3. Schick, B.: Personal communication.
4. Bordley, J. E., and others: Preliminary Observations on Effect of Adrenocorticotropic Hormone (ACTH) in Allergic Diseases, Bull. Johns Hopkins Hosp. **85**: 396, 1949.
5. Rose, B.: Studies on Effect of ACTH on Eosinophilia and Bronchial Asthma, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, 1950, The Blakiston Co.
6. Chase, M. W.: The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin, Proc. Soc. Exper. Biol. & Med. **59**: 134, 1945.
7. Favour, C. B.: Lytic Effect of Bacterial Products on Lymphocytes of Tuberculous Animals, Proc. Soc. Exper. Biol. & Med. **65**: 269, 1947.
8. Fremont-Smith, P., and Favour, C. B.: In Vitro Lysis of Leucocytes from Tuberculous Humans by Tuberculoprotein, Proc. Soc. Exper. Biol. & Med. **67**: 502, 1948.
9. Ragan, C.: The Undesirable Side-effects, Withdrawal Symptoms and Contraindications of the Use of Cortisone and ACTH in Rheumatic Diseases, Bull. Rheumat. Dis. **1**: 5, 1950.

FAMILIAL DEGENERATION OF THE CEREBRAL GRAY MATTER IN CHILDHOOD

With Convulsions, Myoclonus, Spasticity, Cerebellar Ataxia, Choreoathetosis, Dementia, and Death in Status Epilepticus. Differentiation of Infantile and Juvenile Types

Frank R. Ford, M.D., Samuel Livingston, M.D., and Charles V. Pryles, M.D.
Baltimore, Md.

A GREAT many different types of cerebral degeneration in childhood have been described. These conditions are so diversified and our knowledge of them is so incomplete that no adequate classification is yet possible. Nevertheless, we may distinguish certain large groups even though the precise limits of these groups may be somewhat indistinct. For example, we may speak of the lipoid cell degenerations in which there is a specific disintegration of the neurons with deposits of lipoid granules in the cytoplasm. The Tay-Sachs disease, which we may call infantile cerebroretinal degeneration, is the best known and the commonest type. Juvenile types are associated with the names of Bielschowsky, Batten, Spielmeyer, and Vogt. A late form is described by Kufs. In these conditions there is no evidence of a disorder of lipoid metabolism. The process is confined to the nervous system. Very similar changes in the nervous system may occur in Niemann-Pick disease and in infantile Gaucher's disease, however, and in these diseases all the organs of the body are affected.

The term cerebral sclerosis has been applied to another large group of conditions in which the white matter of the brain, especially the myelin, is primarily affected. Many types are known. We may mention the type of Pelizaeus-Merzbacher which begins early in life and runs a long course, the type of Scholz which might be called the subacute, juvenile form, and the acute, infantile form of Krabbe. Schilder's encephalitis periaxialis diffuse, however, is the commonest and best known condition in this group.

There is a third group of degenerations in which the cerebral gray matter is primarily involved. A number of examples are known, but it seems correct to say that we have even less information about these conditions than about the two groups previously mentioned and no detailed classification seems possible at present. The purpose of this paper is to describe four cases of degeneration of the cerebral gray matter which present certain distinctive characteristics. The anatomical findings in two of these cases have been described by Morse.[1]

Case Reports

Case 1 (Ped. A-51076. Path. 20738).—*White girl whose development was always retarded. At 6 years developed petit mal spells. Later, unsteadiness of gait, intention tremor,*

From the Department of Medicine and the Department of Pediatrics of the Johns Hopkins University School of Medicine, and the Epilepsy Clinic of the Johns Hopkins Hospital.

myoclonic movements, convulsions, choreoathetosis, and left hemiparesis. Progressive dementia. Bilateral pyramidal tract signs. Death in status epilepticus at age of 7½ years. Postmortem examination.

M. T., a white girl, was the fifth child of a family of five siblings. The first three children were healthy. The mother then married again and had two children by her second husband. One was the child whose history is now given. The other was the older brother, whose history is given below. The family history contains the case of a maternal uncle who died in status epilepticus in his third decade.

M. T. was born after labor of sixteen hours. Delivery was eventually effected by version and extraction. The child was always backward, dull, and slow. She did not walk until she was 2 years of age and talked imperfectly at the age of 3 years.

At the age of 6 years she began to have head-dropping attacks and also brief periods in which she was out of contact and her eyes would roll up. Twitching of the muscles appeared at about the same time. Within a few months convulsions began. The twitchings became more pronounced. Examination revealed intention tremor and unsteady gait. There were fine, irregular clonic contractions of the muscles which we have termed myoclonus in this and in subsequent histories. Choreoathetoid movements were observed at times. The tendon reflexes were brisk on the right and the plantar response was extensor. Mental deterioration was evident.

During her seventh year, she displayed the same symptoms. Repeated convulsions occurred and finally she was brought into the Harriet Lane Home in status epilepticus. After some days the convulsions ceased. The child remained very dull, however, and the myoclonic twitchings persisted. Left hemiparesis was then evident. During the next month, the hemiparesis disappeared to a large extent and for a time the child could walk. The reflexes were brisk on both sides. The convulsions then recurred and could not be controlled. Myoclonic twitchings were continuous. Finally the child developed status again and died in coma at the age of 7½ years.

All the usual laboratory studies gave negative results. The spinal fluid was normal in all respects. An electroencephalogram was interpreted as showing petit mal and psychomotor complexes without localization. Ventricular air injection revealed no significant abnormalities.

Summary of the Anatomical Findings (Path. 20738-Morse).—The brain displayed very moderate changes on gross inspection. There was some atrophy of the cortex of the left hemisphere and slight dilatation of the left lateral ventricle. The right hemisphere of the cerebellum was smaller than the left. Microscopic examination revealed extensive degeneration of the cerebral cortex most severe in the deeper layers. The neurons showed degenerative changes of variable degree. In some places this process had led to spongy softening. The astrocytes were hypertrophied and microglia cells laden with lipoid droplets were seen. Capillary proliferation was noted in some areas. A moderate loss of myelin was found in the underlying white matter which was regarded as secondary to the cortical destruction. The process was mild in the cortex of the right hemisphere and severe in the cortex of the left hemisphere. The thalamus and corpus subthalamicum were affected on both sides as was the substantia nigra. The striatum was involved on the left but not on the right. The cerebellar cortex and the dentate nuclei were degenerated and many Purkinje cells were lost. The medulla oblongata including the inferior olives was intact and the spinal cord in the cervical region was spared. No inclusion bodies were noted. The process seemed to be purely degenerative and nothing to suggest an inflammatory process or vascular disease was seen.

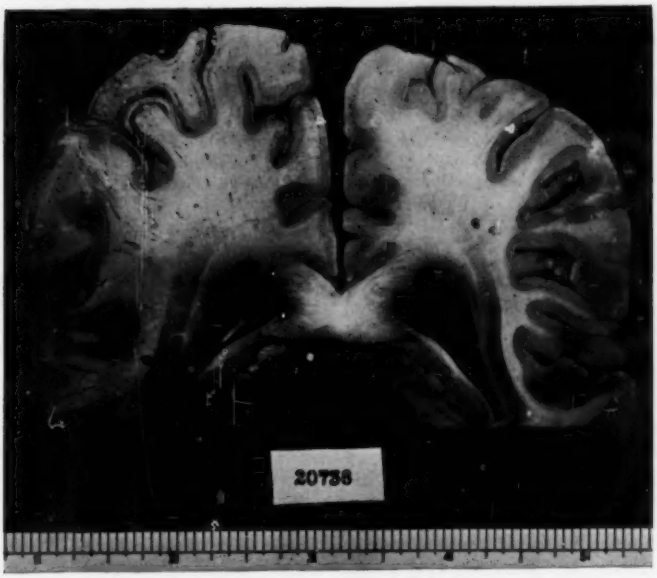

Fig. 1 (Case 1).—Section through the hemispheres showing atrophy of the cortex more evident on the left. (From Morse: Bull. Johns Hopkins Hosp. 84: 116, 1949.)

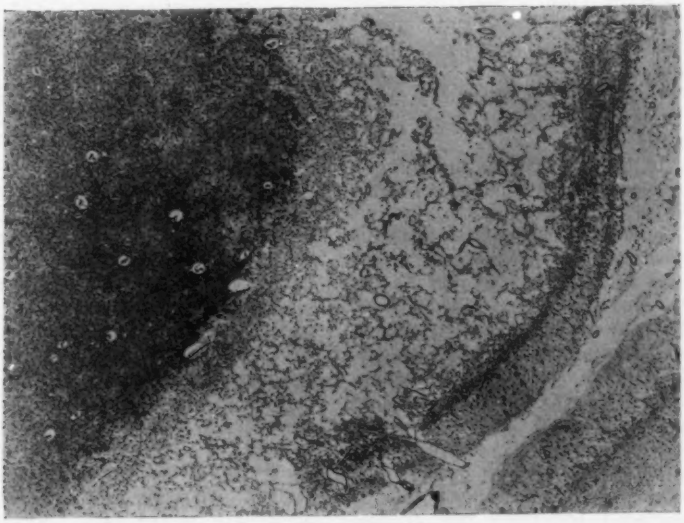

Fig. 2 (Case 1).—Microscopic section showing almost complete destruction of the cortex. (From Morse: Bull. Johns Hopkins Hosp. 84: 116, 1949.)

CASE 2 (Ped. A-24278. Path. 19848).—*White boy, brother of patient previously mentioned. Always retarded. At 6 years petit mal spells and vomiting. Later, myoclonus, intention tremor, choreoathetosis, and right hemiparesis. Convulsions. Mental deterioration. Death in status at age of 8 years. Post-mortem examination.*

G. T., the fourth child, was born by difficult labor, and artificial respiration was required for thirty minutes before he could be induced to breathe. He was slow in his development. He did not walk until he was 2 years of age and talked first at the age of 3 years.

It is stated in one note in the history that head-dropping attacks started at the age of 2½ years but this is doubtful. He was examined at the age of 4 years. The complaint at that time was that of episodes of vomiting which were followed by sleep of two hours' duration. Nothing could be found on examination except for a suggestion of spasmodic torticollis.

Perhaps, the onset of the progressive process occurred at the age of 6 years. He began to have numerous head-dropping attacks at that time and would fall to the floor in some of these. Jerky movements of the extremities, i.e., myoclonus appeared. He grew clumsy in his movements and his gait was unsteady. His mental condition deteriorated. He frequently vomited. Large movements of the extremities suggestive of choreoathetosis were sometimes seen.

At the age of 8 years, the child was brought into Harriet Lane Home in status epilepticus. The seizures involved the right side. He was in coma. After three days, the seizures stopped. He was then found to show right hemiparesis with reduction of the tendon reflexes, intention tremor, and mental deterioration. The myoclonic twitchings persisted, but there was gradual improvement in the control of the right arm and leg. The reflexes became brisk.

Some five weeks after the first series of seizures, the patient fell into convulsions once more. These lasted for several days. When they ceased, the child seemed to be blind, deaf, and demented. The myoclonus became continuous and bilateral though it was more prominent on the right side. Death occurred in status at the age of 8 years.

Laboratory studies were negative. The spinal fluid was normal. The ventriculogram revealed no definite abnormalities. The electroencephalogram showed a spike and wave pattern with marked irregularity and slow rhythm.

Summary of the Anatomical Findings. (Path. 19848-Morse).—The process was of the same type as in the previous case, but less extensive and less destructive. No doubt, it was merely less advanced. The study was also less complete. It should be said that the optic nerves and retinae, which had not been examined in the preceding case, were sectioned and found to be normal.

CASE 3 (Ped. 83173. Path. 14380).—*Convulsions at 6 months. Myoclonic contractions. Left hemiparesis, and later, bilateral spasticity. Progressive deterioration with death at 15 months in status epilepticus. Post-mortem examination.*

M. J., a Negro girl 6 months of age, began to have convulsions which were sometimes bilateral and sometimes confined to one side or the other. These became more frequent and were associated with twitchings of the muscles which sometimes persisted for days. Before the end of the first year it was evident that the child was deteriorating. She was no longer able to sit up or even to hold up the head. She seemed to be blind and did not respond to auditory stimuli. There was occasional vomiting and progressive loss of weight. The mother was ignorant and the history possibly incomplete.

At the age of 14 months the child was brought to Johns Hopkins Hos-

pital. She was then well developed but somewhat underweight. The temperature was normal. There was no evidence of any mental development. She seemed to be deaf and blind. The optic fundi showed no changes, however, and the pupils reacted to light. There was generalized muscular rigidity with increased tendon reflexes and bilateral ankle clonus. The rigidity was much more severe on the left side. She was quite helpless and could not sit up or even hold up her head.

The child rapidly grew worse. Frequent convulsions occurred, often on the right side. There were almost continuous myoclonic contractions* involving the face as well as the extremities. These might be on one side or the other. Vomiting occurred from time to time. Death occurred at the age of 15 months.

All the usual laboratory studies were negative. Pneumoencephalograms were made. These showed slight enlargement of the right lateral ventricle and large collections of air over the cortex of the right hemisphere. The spinal fluid was quite normal.

Post-mortem examination revealed nothing of importance except for the changes in the central nervous system. The brain weighed only 700 grams. The cortical gray matter of the right hemisphere was grossly atrophied and soft. In the left hemisphere there was only very slight atrophy. The white matter and the basal ganglia appeared to be normal though the right ventricle was somewhat larger than the left. The entire vascular system was normal. Histological studies showed extraordinary loss of neurons in the cortex of the right hemisphere. This seemed to involve almost all lobes of that hemisphere. The process was most destructive in the third and fourth layers of the cortex where nothing was left except for a spongy reticulum of glial tissue which was traversed in places by bundles of nerve fibers which were relatively well preserved. There were moderate numbers of microglia cells containing lipoid products but no infiltration of lymphocytes or plasma cells. In the left hemisphere the process was much less severe and, no doubt, just beginning. It seemed to be of essentially the same nature as that on the right. There was only moderate loss of neurons in the cerebral cortex but those remaining were often shrunken. Microglia cells were present and a mild reaction of the astrocytes was observed. The white matter of both hemispheres seemed to be intact. The basal ganglia showed no definite alterations. The cortex of the cerebellum, however, showed well marked degeneration. Many Purkinje cells were destroyed and the cells of the superficial molecular layer were almost all lost. No doubt, cerebellar ataxia was present but masked by the rigidity and paralysis. The retinae and optic nerves showed no changes. No inclusion bodies were noted.

*In an abstract published previously, it was stated erroneously that myoclonus was absent.

CASE 4 (Ped. A-62634).—*White boy always retarded in his development. At 4 years developed convulsions and then myoclonus on the left. At 5½ years dementia, left hemiplegia, and choreoathetosis on the right as well as bilateral Babinski sign. Death at age of 6 years. No post-mortem examination.*

A. W., a white boy, was born by hard labor of twenty-nine hours' duration. His early development was always retarded. He had pertussis at 7 months of age and chicken pox at the age of 5 years. A male sibling died at the age of 9 months with fever and convulsions. There were four other siblings living and well.

In November, 1947, when the child was 4 years old, he had a series of convulsions and was in coma for ten days. About three months later, he had another series of convulsions, some of which were confined to the right side. After this second episode there were muscular twitchings on the right

side of the face and in the right extremities which persisted for several weeks.

A third series of convulsions developed after an interval of two months. This coincided with the development of varicella. The temperature was normal, however. The convulsions could not be controlled until ether was employed. The same statement is made in regard to the previous convulsions. Following this illness the patient displayed muscular twitchings on the left side. The convulsions recurred and the boy became helpless and was confined to bed.

At the age of 5 years the patient was brought to the Johns Hopkins Hospital. He was found to be well nourished and well developed but was in such a state of stupor or dementia that he could not cooperate in the examination. He did not respond to auditory stimuli and showed no voluntary activity. The pupils reacted to light and the optic fundi showed no changes. There was a flaccid left hemiplegia which seemed to be complete. The right arm showed complex movements. Some of these were myoclonic and some resembled choreoathetosis. The reflexes were not exaggerated but the plantar responses were extensor on both sides.

All the usual laboratory tests gave negative results. A pneumoencephalogram revealed normal ventricles and there was no evidence of cortical atrophy. An electroencephalogram revealed generalized high voltage slow spike and wave forms and a spike focus in the right occipital region which spread over the cortex. The spinal fluid was normal.

In spite of intensive medication with many different drugs the myoclonic contractions persisted.

He was sent home after forty-seven days in the hospital without any change in his condition. Thereafter he remained in a state of coma with constant myoclonic contractions until death at the age of 5½ years. No post-mortem examination was made, but the clinical features were so typical that we felt justified in including this case.

DISCUSSION OF CASES FOUND IN MEDICAL LITERATURE

Alpers[2] has reported the case of an infant whose symptoms began at the age of 3 months and who died at 5 months. There were convulsions, hyperkinesis, and attacks of generalized rigidity of the musculature. The tendon reflexes were increased. A careful and complete examination of the brain was made. Evidences of defective development of the cortex were noted. There was also widespread degeneration of the gray matter. This process involved almost the entire cerebral cortex being most severe in the third and fourth layers. In places there was spongy softening, and in other areas, merely histological evidences of neuronal degeneration. Proliferation of the astrocytes and a variable degree of gitter cell production were noted. Striking proliferation of capillaries was evident in areas in which the damage was severe. The striatum, pallidum, and the thalamus were involved but the cerebellum was spared. Lesions were seen in the pons.

Alpers cites the case of Somoza[3] which apparently has never been published. This child died at the age of 8 months. Hyperkinesis, choreiform movements, and opisthotonos are mentioned. The anatomical changes, Alpers states, were almost identical with those of his case, but the substantia nigra was involved, whereas, in his case, it was spared.

Freedom[4] has also reported a case in which the patient died at the age of 19 years. She was always backward. Convulsions began at the age of 5 years. Muscular twitchings were

noted. There was progressive mental deterioration. The knee and ankle jerks were exaggerated and Babinski's sign was found bilaterally. Mild athetoid movements were seen. The cortex at autopsy showed extensive damage of the type described by Alpers. It was most advanced in the occipital region and in the island of Reil. The striatum, pallidum, hypothalamus, and dentate nucleus were all involved.

A valuable paper has recently been published by Christensen and Krabbe[5] who reported the case of a child who was found to be backward in development at 8 months. Progressive deterioration became evident at 22 months. Later, the child displayed spasticity, ataxia, myoclonus, and inability to speak. There were never any convulsions. Death occurred at the age of 2½ years. Examination of the nervous system revealed disorganization of the cortex which was attributed to a developmental defect and a destructive process similar in all essentials to that described by Alpers. The latter was confined to the cerebral cortex which was histologically altered everywhere except for the cornu ammonis. As in the cases previously mentioned, the cortical degeneration was marked by destruction of neurons and by proliferation of astrocytes and microglia cells. No changes were found in the cerebellum, basal ganglia, brain stem, or white matter. Christensen and Krabbe review the cases mentioned above and Case 3 of ours, which has been published before. They conclude that all are of essentially the same nature.

In this connection the family studied by van Bogaert[6] should be mentioned. In all, six individuals were affected in three generations. Both males and females were involved. In some individuals, convulsive seizures were the only symptoms. In three, however, the whole picture of the disease was manifest. The clinical symptoms included epileptic phenomena, chiefly petit mal, vertigo, and psychic equivalents, myoclonic movements, chiefly in the proximal muscles, involuntary movements resembling choreoathetosis but at times similar to those of torsion spasm, and large movements resembling the bradykinesias seen in epidemic encephalitis. In these three cases, the onset was usually between the ages of 2 and 3 years and death occurred between 10 and 17 years. Post-mortem examination revealed degeneration of the deeper layers of the cerebral cortex in the frontal region and the motor areas. Degeneration of the striatum and pallidum was also present and the striatum presented the appearance known as état marbré. The bulbar olives were degenerated.

The familial myoclonus epilepsy of Unverricht[7] should also be mentioned here. This disease is likely to begin between the ages of 6 and 13 years and has been said to be more frequent in girls than in boys. According to Lundborg[8] it behaves as a Mendelian recessive characteristic. Convulsions mark the onset and the myoclonus appears one to five years later. The muscular twitchings are most evident in the proximal muscles of the extremities and are symmetrically distributed as a rule. They are quite irregular and asynchronous on the two sides. At first they are small and do not move the extremities. Later, they may become more powerful and may actually throw the patient to the floor. Mental deterioration invariably occurs

and ends in dementia. After some years ataxia of cerebellar type develops and Parkinsonian rigidity as well. There may be evidences of pyramidal tract damage. The course seems to average ten to twenty years. A variety of anatomical changes are described. These have been analyzed by Hodskins and Yakolev[9] who collected eighteen post-mortem examinations of the nervous system in cases of this type which had been published between 1911 and 1928. In most of these cases there were degenerative changes in the dentate nucleus of the cerebellum, thalamus, substantia nigra, and red nucleus. In many instances the cerebral cortex was involved. A very characteristic feature was the presence of amyloid bodies in the nerve cells which were especially numerous in the structures mentioned above. In other instances there seems to have been nothing characteristic about the process except, perhaps, its distribution.

On the basis of these statements, we believe we are justified in saying that our cases are quite different from those of Unverricht and also different to some extent from those of van Bogaert. These conditions are, therefore, excluded from the following discussion. With these omissions we find ourselves with a fairly homogenous group of cases for our consideration.

ANALYSIS OF THE ANATOMICAL FINDINGS

In every case there has been extensive degeneration of the cerebral cortex. This may be mild and evidenced only by histological changes in the neurons, but eventually progresses to cause spongy areas of softening. It is invariably most severe in the deeper layers of the cortex. There is destruction of neurons and proliferation of astrocytes and microglia cells. In some areas capillary proliferation is observed. There is no evidence of an inflammatory process or of vascular disease. It seems to be a purely degenerative condition. In our cases the cortex of one hemisphere was involved more severely than the other. Only secondary changes were found in the white matter. No inclusion bodies were found.

Alpers and Christensen and Krabbe mention disorganization of the cortex which they attribute to disturbances of development and distinguish from the progressive degeneration which develops later.

In the case of Christensen and Krabbe only the cerebral cortex was involved. In other cases, however, a similar degenerative process was found in the striatum, thalamus, corpus subthalamicus, substantia nigra, and sometimes the pallidum. The cerebellum is also frequently involved. Apparently the degeneration of the cerebral cortex is the only constant finding.

ANALYSIS OF THE CLINICAL FEATURES

We find nine cases available for analysis. These seem to fall into two groups.

We may place in an *infantile group* a total of four cases including those of Alpers, Somoza, Christensen and Krabbe, and our Case 3. The onset was always before the end of the first year and only one patient lived to the age of 2½ years. Convulsions are recorded in all cases except that of Christensen and Krabbe. Myoclonus was noted in two cases. Hyperkinesis was mentioned in two cases but not fully described. Choreoathetosis is

not always recognized in babies unless it is severe. Rigidity was probably present in all. Ataxia is noted only once. It seems probable, therefore, that the diagnosis cannot often be made with confidence in this age group. The typical pattern may not be apparent. One may see merely progressive deterioration, convulsions, and rigidity.

The *juvenile group* included four cases, that of Freedom and our Cases 1, 2, and 4. The onset was between the ages of 3 and 6 years, and death occurred between the ages of 6 and 19 years. In four cases, the children's early development was said to be retarded. In our cases, this was noted in every instance in which a clear history was elicited. The onset of the progressive phase of the disease was marked by convulsions and petit mal (head-dropping) as a rule. In one case ataxia was said to be the initial symptom.

The *convulsions* were restricted to one side or the other and were likely to occur in series from time to time. If the convulsions first appeared on the right side, they might involve the left side in the next episode. However, generalized seizures occurred also. These convulsions were hard to control and the standard drugs used both singly and in combination seemed to have no effect.

Fine, muscular twitchings, which we have termed myoclonus, were closely associated with the convulsions. These would be constantly present for days or weeks. They were most evident in the extremities but also involved the face and, in one case, the diaphragm. Increasing myoclonus seemed to herald the approach of convulsions. After a series of convulsions, myoclonus was likely to be active for a time and then diminish. The myoclonus was usually more pronounced on one side or the other, and, in most instances, was more active on the side of the convulsions. One might well term these twitchings epilepsia partialis continua.

Hemiparesis often followed a series of unilateral convulsions and was then found on the affected side. At first, the weakness was associated with flaccidity of the muscles, but spasticity soon developed. There was sometimes partial recovery after such an episode but each series of convulsions seemed to leave a residuum so that there was eventually bilateral hemiplegia. In all our patients, one side was affected more severely than the other but other authors do not note this asymmetry.

Cerebellar ataxia was never a prominent feature in these cases but was noted in three. Probably it is soon masked by the increasing weakness and spasticity. Perhaps, it was more evident in the early stages of the diseases before the patients were examined.

The *choreoathetosis* was seen when the disease was well advanced but seems to have disappeared later. It was never severe.

These children seemed to be deaf and blind toward the end, but their mental condition was such that one could not be sure. As a rule, the pupils reacted to light and the optic discs and retinae were normal. On several occasions it was noted that the pupils failed to react to light, but it is probable that this was merely a postconvulsive phenomenon for when tested later, a reaction was elicited. One is inclined to say that if blindness was really present, it must have been of cortical origin. In the two patients in whom the retinae and optic nerves

were examined at post mortem they were found to be normal.

These children were frequently seen in states of stupor or coma following convulsions and at such times it was impossible to estimate how much mental deterioration was present. However, it cannot be doubted that there was progressive loss of mentality and eventually dementia.

The electroencephalogram did not reveal anything characteristic. One report reads, "Abnormalities in all leads. High voltage waves of 1 to 2 per second." Another report describes "A spike focus in the right occipital cortex and petit mal variants." A third note mentions "Petit mal and psychomotor complexes without localization." A fourth report reads, "Spike and wave pattern with slow rhythm."

The pneumoencephalogram was reported as negative, as showing mild dilatation of one ventricle, and as revealing normal ventricles with enlargement of the cortical sulci. The last would seem to be typical. We have seen it twice.

The spinal fluid showed no changes. In each case laboratory studies were made to rule out syphilis, lead poisoning, and metabolic disturbances, such as hypoglycemia and tetany. All such studies were negative.

In general, one may say that there is a very good correlation between the clinical signs and the anatomical lesions. The developmental defects of the cortex noted by Alpers and by Christensen and Krabbe, no doubt, explain the retardation of early development. The convulsions, spasticity, and dementia must be due to the cortical degeneration. If these children are really blind and deaf, we believe that the cortical lesions are responsible. Grinker and associates[10] found evidence in an electroencephalographic study that myoclonus arises in the cerebral cortex and we are inclined to agree with this view at least in regard to these cases. The hemiplegia is easily explained by the greater degeneration of one cerebral cortex than the other. The choreoathetosis is, no doubt, to be attributed to degeneration of the striatum and the ataxia to involvement of the cerebellum. We have never recognized Parkinsonian rigidity which might be attributed to damage to the pallidum but this might have been present in the terminal stages of the disease.

SUMMARY

We have described four cases of degeneration of the cerebral gray matter in childhood running a progressive course to a fatal outcome. The clinical features of this condition include convulsions, myoclonus, spasticity, choreoathetosis, cerebellar ataxia, and dementia. It is sometimes a familial disease.

There is always degeneration of the deeper layers of the cerebral cortex and sometimes degenerative changes in the basal ganglia of the forebrain, thalami, and cerebellum.

We have distinguished *infantile* and *juvenile* types of this disease. Christensen and Krabbe term this condition *poliodystrophia cerebri progressiva infantilis*. Perhaps, we might designate it in English as *degeneration of the cerebral gray matter of Alpers*.

REFERENCES

1. Morse, Wm. I., 2nd: Hereditary Myoclonus Epilepsy. Two Cases With Pathological Findings, Bull. Johns Hopkins Hosp. 84: 116, 1949.

2. Alpers, B.: Diffuse Progressive Degeneration of the Cerebral Gray Matter, Arch. Neurol. & Psychiat. **25**: 469, 1931.
3. Somoza: Abstracted by Alpers. Apparently not published.
4. Freedom, L.: Cerebral Birth Palsies, Arch. Neurol. & Psychiat. **26**: 524, 1931.
5. Christensen, E., and Krabbe, K. H.: Poliodystrophia Cerebri Progressiva Infantilis, Arch. Neurol. & Psychiat. **61**: p. 28, 1949.
6. Van Bogaert, L.: Sur une variéte non décrite d'affection familiale—L'Epilepsie myoclonique avec choreo-athetose, Rev. neurol. **2**: 385, 1929.
7. Unverricht, H.: Ueber familiäre Myoclonie. Deutsche Ztschr. f. Nervenheilk. **7**: 32, 1895.
8. Lundborg, H.: Der Erband der progressiven Myoclonus-Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **9**: 353, 1912.
9. Hodskins, M. B., and Yakolev, P. I.: Anatomico-Clinical Observations on Myoclonus in Epileptics and on Related Complexes, Am. J. Psychiat. **9**: 827, 1930.
10. Grinker, R. R., Serota, H., and Stein, S. I.: Myoclonic Epilepsy, Arch. Neurol. & Psychiat. **40**: 969, 1938.

CONGENITAL DUODENAL OBSTRUCTION

A Report of Two Cases Emphasizing Postoperative Course

Lieutenant (jg) C. James Krafft (MC) USNR, Lieutenant (jg) Robert Ford Neal (MC) USN, and Lieutenant Arvin T. Henderson (MC) USN

CALDER[1] described the first case of duodenal obstruction in 1733. In 1922, Davis and Poynter[2] reviewed the literature of 392 cases of congenital intestinal obstruction; during this time the mortality remained virtually 100 per cent. With the improvement of diagnosis and surgical technique in the past two decades, the mortality has dramatically declined. It is imperative that diagnosis be made early when surgical intervention is optimal.

Recently we diagnosed and treated two patients with duodenal atresia. The problems arising from the postoperative care of these infants merit presentation, as only brief discussions of this phase of management were found in the literature. Our paper, therefore, will be confined largely to diagnosis and postoperative care, since these are the pediatrician's chief concern.

Duodenal obstruction has been discussed by Forshall[3] and has been presented by Ladd.[4] Usually the presenting symptom is vomiting within the first thirty-six hours or shortly after feeding is instituted. Force of the vomiting increases to become projectile, and if the obstruction is distal to the ampulla of Vater, bile is present in the vomitus. There is usually passage of meconium stools. Dehydration is rapid, and with it progressive weight loss occurs. Of striking interest, in contrast to pyloric stenosis, is the lack of hypertonicity and of hunger-pang symptoms. The sucking reflex is weak and increasing apathy is apparent.

The physical examination reveals a degree of weight loss and dehydration dependent upon the duration of symptoms. There is frequently fullness of the epigastrium with tympany, while the lower abdomen is scaphoid and dull to percussion. Peristaltic waves may be seen traversing the epigastrium.

Roentgenographic evidence is an important adjunct to the history and physical examination in the diagnosis of this condition. Although some papers recommend the introduction of radiopaque substances in the stomach, the consensus is that this is definitely contraindicated and dangerous. Barium suspensions are considered inadvisable in that they may be vomited and aspirated or may obstruct the operative stoma. Plain films of the abdomen taken within the first 12 to 24 hours of life are limited because the stomach and duodenum may be only slightly dilated with gas. Mellins and Milman[5] advocated aspiration of the stomach followed by insufflation of air in sufficient quantities to dilate the proximal duodenum. This technique will be discussed subsequently in this paper.

Farber's test[6] for epithelial cells in the meconium is suggested by many,

From the U. S. Naval Hospital, San Diego, Calif.

The opinions or assertions contained in this article are the private ones of the writers and are not to be construed to be official or reflect the views of the Navy Department or naval service at large.

We wish to give credit to Commander Sol M. Abelson, Head of Pediatric Department, U. S. Naval Hospital, San Diego, and to Dr. William W. Belford, Civilian Consultant in Pediatrics, for their guidance, comments, and criticism in the preparation of this paper.

but found inconclusive by others.[7] We found this test relatively unnecessary since our diagnosis seemed complete with the above criteria.

Forshall[3] determined the incidence of duodenal obstruction to be 1 in 20,000 live births. No sex preference and no hereditary influences were noted. Incidence is increased among premature infants, and from our review of the literature five cases have been reported among Mongolian idiots. One of the cases reported herein (S.K.) is apparently the sixth such case. Most patients, however, appear healthy at birth. About 15 per cent of these patients are found to have concomitant obstructive lesions lower in the intestinal tract, a fact which must be considered at surgery.

As soon as diagnosis can be made, surgery must not be delayed. It has been shown that an infant within its first 48 hours can withstand surgery more readily than he can a week or so later.[8] Dehydration and electrolyte imbalance should be rapidly corrected preoperatively by intravenous fluids, and blood transfusion given if anemia is present following rehydration. Vitamin K injections should be administered, and calcium therapy is often indicated. The stomach should be lavaged, aspirated, and the tube left in place during surgery. Oxygen administration is frequently helpful.

The type of operation most widely preferred is a duodenojejunostomy. This is stated to be far more satisfactory than a gastroenterostomy, since the latter causes loss of appetite and failure to gain weight properly,[4] also demonstrated by the following cases.

CASE REPORTS

CASE 1 (J.K.W.).—A newborn white male admitted to the hospital by birth on Nov. 29, 1950, was the product of a full-term pregnancy and normal delivery. His birth weight was 6 pounds, 13½ ounces. The baby appeared normal at birth and routine nursery care was instituted, with breast-feeding at 24 hours of age. From the first day of life the mother noted increasing regurgitation. The diagnosis of tracheoesophageal fistula was eliminated by unobstructed passage of a tube into the stomach. On the third day the baby was placed on supplementary formula because of approximately 1 pound loss from birth weight. Despite the formula, the baby continued to regurgitate moderate amounts, but still did not appear to be in any distress. Feeding of a more dilute formula on the fourth day produced no improvement. Subsequently, on the same day, because of continued vomiting, stomach aspiration before each feeding was ordered. The aspirations yielded from 30 to 50 c.c. of green fluid every three hours. On the fifth day of life, x-ray examination of the abdomen revealed two small areas of gas which were not diagnostic. Following this, the stomach was insufflated with 30 c.c. of air per gavage tube.[5] Repeat films (Fig. 1) were taken which revealed a stomach bubble and a large bubble in what appeared to be a dilated segment of proximal duodenum, with absence of gas elsewhere in the gastrointestinal tract. Our clinical impression from the x-ray findings and the history was duodenal atresia or stenosis.

Preoperatively the baby was placed on nothing by mouth and the stomach was aspirated every three hours. His weight was 5 pounds 10 ounces and he appeared moderately dehydrated. He was noted to have prominence of the upper abdomen which was tympanitic and a flat lower abdomen which was dull to percussion. There had been no stools noted except the meconium. On the fifth day a small amount of "fecal" material was obtained on digital rectal examination. A Farber test was not done. Parenteral fluids consisting of a total of 300 c.c. were given in the next twenty-four hours, of which 100 c.c. was normal saline.

Surgery was performed on the baby's sixth day of life (Dec. 5, 1950). The surgeon found an acute angulation of the second portion of the duodenum. No lumen could be demonstrated in this segment either by expression of gas or by passage of a small rubber catheter. The diagnosis of duodenal atresia was thus confirmed and a posterior gastroenterostomy was done. One hundred cubic centimeters of whole blood were given during surgery, following which the infant was returned to the ward in apparently good condition.

Fig. 1.

The postoperative course was complicated by a prolonged period of frequent emesis and feeding difficulties. Treatment consisted of stomach aspiration and parenteral fluids including electrolytes for a period of two weeks postoperatively. The patency of the anastomosis was demonstrated by x-ray examination on the fourth postoperative day. In spite of this, stomach aspirations yielded 20 to 30 c.c. of bile-stained fluid each time. The baby was maintained on intravenous infusions of glucose, saline, and protein hydrolysate supplemented by Ringer's lactate by hypodermoclysis. (Fig. 2.)

A second exploratory operation was contemplated. On the twelfth postoperative day a barium meal was given which offered an explanation for our lack of success. Part of the barium went through unobstructed, but the bulk of it remained in a large dilated duodenal bulb. By placing the infant on his left side after each feeding, retention in the duodenum was minimized. By the end of the second postoperative week he was retaining adequate formula by mouth.

Although he had an excellent appetite, normal stools, and adequate caloric intake, the infant appeared marasmic and weighed one pound under birth weight at the end of his first month. Although the stools contained trypsin, pancreatin was added to the diet in the form of Panteric granules,

and calorie intake was increased. Gradual weight gain up to 6 pounds, 5½ ounces permitted the baby to be discharged home.

Follow-up study indicates that the blind duodenal bulb may continue to cause trouble and a revision of the original operation may be necessary. At the time of writing this paper, however, he has regained his birth weight and has no more vomiting. Further surgery might have been obviated if a duodenojejunostomy had been done, but this procedure was technically impossible at the time of original operation.

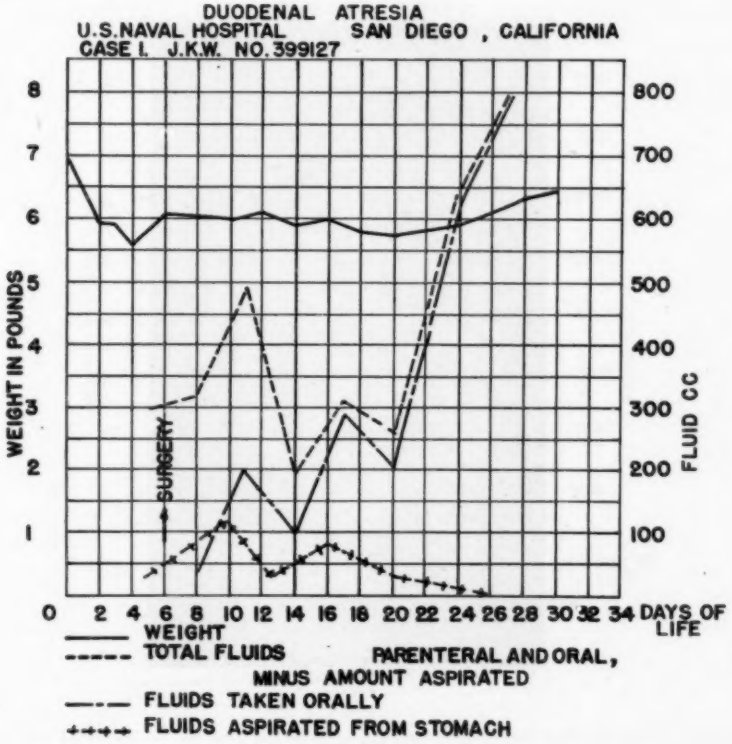

Fig. 2.

Case 2 (S.K.).—A newborn white female, birth weight 4 pounds, 11 ounces, was admitted to this hospital from a neighboring activity on July 25, 1950, with history of vomiting "coffee-colored" material. She was delivered by outlet forceps at twenty-eight weeks' gestation following an uneventful pregnancy. The baby was 36 hours old at the time of admission to this hospital. Feeding had been started about six hours prior to admission, and the baby had been transferred because of vomiting which began even prior to the first feeding.

At the time of admission she was continuously regurgitating dark brown fluid which appeared to contain blood and bile. Her weight was 4 pounds, 5 ounces. Hemorrhagic disease of the newborn was considered (with or without gastric ulceration). Accordingly, she was placed on nothing by mouth, given one transfusion of 50 c.c. of

whole blood, and started on fluid by hypodermoclysis. Meconium stools appeared normal. X-ray examination of the abdomen revealed gas in the stomach and proximal portion of the duodenum with absence of gas elsewhere in the gastrointestinal tract (Fig. 3). Because of x-ray findings and persistent vomiting, a diagnosis of duodenal obstruction was made. A concurrent diagnosis of Mongolism was also entertained.

Fig. 3.

Surgery was performed when the infant was 60 hours of age. The surgeon found a tremendously dilated stomach and duodenum, and the proximally dilated duodenum could be followed to the retroperitoneal portion. It was dilated to a diameter of 1½ to 2 inches, with the point of atresia located near the ligament of Treitz. A gastroenterostomy was performed. Postoperative condition was fair.

She was started on water by mouth at twenty-four hours postoperatively and retained small amounts. This was supplemented with parenteral fluids. Since on the second postoperative day the patient began vomiting, intermittent stomach aspirations were resumed. The patient was maintained on gastric aspiration and parenteral fluid until the fifth postoperative day when skim milk was started by mouth. At this time, patency of the anastomosis was demonstrated by an x-ray examination of the abdomen which showed gas to be present throughout the bowel. Milk feedings were retained well and aspirations decreased in amount. On the seventh postoperative day aspiration was discontinued. (Fig. 4.) The baby was discharged home on the sixteenth postoperative day, eating and gaining well, and with normal stools.

Subsequent follow-up at the time of writing confirmed the suspicion of Mongolism. The gastrointestinal tract was apparently functioning fairly

well, but weight gain has not been completely up to normal expectation.

DISCUSSION

With regard to the type of surgery indicated in these cases, we feel that Case 1 amply illustrates the disadvantage of the gastroenterostomy. This infant probably suffers a chronic inactivation of his duodenal enzymes since secretions from the dilated, blind duodenal bulb necessarily must traverse the stomach to reach the jejunum. Pancreatin may partially rectify this difficulty. The postoperative management is vitally influenced by the type of surgery performed.

The necessity and wisdom of stomach aspiration in these cases can be seen from the graphs and case histories. We would like to suggest the desirability of intermittent aspiration as opposed to continuous aspiration. The former permits some absorption during the two- to three-hour interval and decreases the danger to the infant's respiratory tract from aspiration. Early intermittent aspiration should be started preoperatively as soon as the diagnosis is made and continued even after feedings are started by mouth.

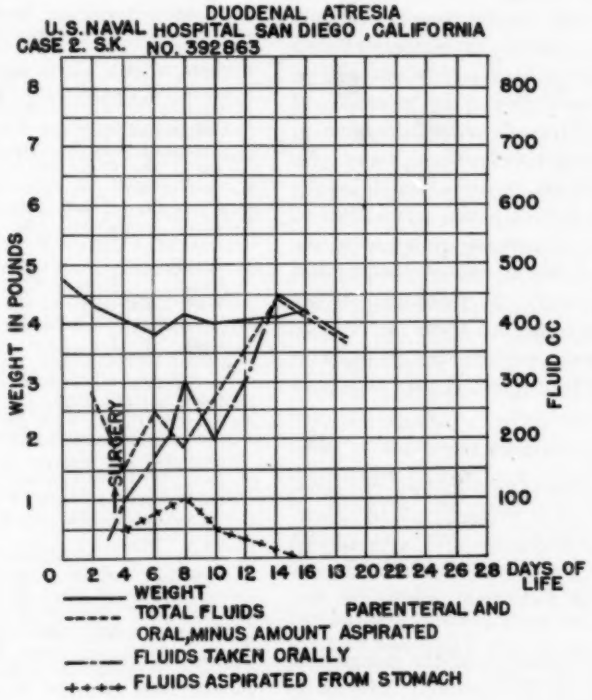

Fig. 4.

Parenteral fluid administration offers no special considerations; only these things are borne in mind: One must replace the measured amount aspirated with chloride-containing fluids, in addition to the basal requirements

of fluid, electrolyte, and calories. Protein hydrolysate and whole blood are useful in generous amounts.

With regard to roentgenographic studies and interpretation, we might add that one of us (R.F.N.) conceived the idea of stomach insufflation with air (Case 1) unaware of the report of Mellins and Milman[5] previously mentioned. We wish to further emphasize the gratifying results from this simple procedure (Fig. 1). It is accomplished by evacuation of the stomach with a gavage tube followed by injection of air and taking of immediate films in anteroposterior and oblique views. No better contrast medium could be desired. In Case 2, serial x-ray films of the abdomen were our guide as to the function of the enterostomy stoma and the beginning of feedings. The barium studies in Case 1 on the twelfth postoperative day were helpful and did not produce any untoward symptoms.

SUMMARY

Two cases of congenital duodenal obstruction are presented with a survey of the literature and with special reference to postoperative management. The following points are emphasized:

1. Air insufflation of the stomach as advocated by Mellins and Milman is simple to do and of great value.

2. Preoperative and postoperative intermittent stomach aspiration is desirable.

3. Parenteral fluids including electrolytes are given in adequate amounts to replace fluid loss and maintain calorie intake.

4. The disadvantages of gastroenterostomy as the operative procedure are exemplified; perhaps a duodenojejunostomy (as advocated by Ladd) would prevent many of the postoperative difficulties seen in these cases.

REFERENCES

1. Calder, J.: Two Examples of Children Born With Preternatural Conformations, from the Great Medical Essays and Observations, Edinburgh **1**: 203, 1733.
2. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestine, Surg., Gynec. & Obst. **34**: 35, 1922.
3. Forshall, Isabella: Duodenal Obstruction in the Newborn, Brit. J. Surg. **35**: 58, 1947.
4. Ladd, W. E.: Congenital Duodenal Obstruction, Surgery **1**: 878, 1937.
5. Mellins, H. Z., and Milman, Doris H.: Congenital Duodenal Obstruction, Roentgen Diagnosis by Insufflation of Air, Am. J. Dis. Child. **72**: 81, 1946.
6. Farber, S.: Congenital Atresia of the Alimentary Tract; Diagnosis by Microscopic Examination of the Meconium, J. A. M. A. **100**: 1753, 1933.
7. Madding, G. F., Everhart, M. W., and Heath, J.: Congenital Duodenal Atresia With Malrotation of the Intestine, Ann. Surg. **131**: 433, 1950.
8. Ladd, W. E.: Béla Schick Lecture: Choice of Time and Type of Operation in Surgery of Early Life, J. Mt. Sinai Hosp. **10**: 389, 1943.
9. Benson, C. D., and Penberthy, G. C.: Congenital Duodenal Obstruction, Arch. Surg. **56**: 58, 1948.
10. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders Co., pp. 25-43.
11. Kaplan, L.: Congenital Duodenal Obstruction Due to Atresia of the Duodenum, Am. J. Surg. **79**: 452, 1950.
12. Glaser, S.: Congenital Occlusion of the Duodenum, Brit. M. J. **2**: 712, 1948.
13. Swenson, O., and Ladd, W. E.: Surgical Emergencies of the Alimentary Tract of the Newborn, New England J. Med. **233**: 660, 1945.
14. White, C. S., and Collins, J. L.: Congenital Duodenal Obstruction, Arch. Surg. **43**: 858, 1941.
15. Stetten, De W.: Duodenojejunostomy for Congenital, Intrinsic, Total Atresia at the Duodenojejunal Junction, Ann. Surg. **111**: 583, 1940.
16. Saunders, J. B. de C. M., and Lindner, H. H.: Congenital Anomalies of the Duodenum, Ann. Surg. **112**: 321, 1940.
17. Leitch, P.: Duodenal Atresia in Newborn Infant, Brit. M. J. **2**: 885, 1945.
18. Sumner, W. C., and Morris, K. A.: Duodenal Atresia in Newborn: Case Report, Am. J. Surg. **68**: 120, 1945.

SPATIAL VECTORCARDIOGRAPHY IN CHILDREN: AN ANALYSIS OF HIGH R WAVES IN RIGHT-SIDED CHEST LEADS

RICHARD P. LASSER, M.D., AND ARTHUR GRISHMAN, M.D.
NEW YORK, N. Y.

THE unipolar precordial electrocardiogram of infants and children differs from that of adults in respect to the ratio of R to S waves in right precordial leads, and in the direction of the T waves.[1, 2, 3, 4, 5] The adult pattern consists of a small r deep S wave in right anterior chest leads followed by inverted or upright T waves. As leads V_2 to V_6 display a progressive increase in the size of the R wave, a proportionate decrease in the amplitude of the S wave is seen. In infants and children, up to approximately 3 years of age and, at times, even later, the R wave in lead V_1 is much taller than commonly seen in adults and may equal or even exceed the amplitude of the S wave in the same lead. The S wave is found to persist in all of the conventional six precordial leads. Although the ratio of R to S in V_1 may be equal to or exceed unity, it is invariably less than one in normal adults. In a recent study, this pattern was found to be present in about 75 per cent of children from birth to 2 years of age, in 25 per cent of the age group from 3 to 5 years, and 10 per cent in the age group from 5 to 13 years. Complete reversal of the adult pattern, however, was observed only in children below the age of one month, i.e., Rs complexes in V_1 with r^S complexes in V_6.[4] T waves are commonly found to be inverted in chest leads as far to the left as V_3 and occasionally V_4.

From the Cardiographic Department, The Mount Sinai Hospital.

The pattern of precordial leads in young children may offer considerable difficulties in the electrocardiographic diagnosis of pathological right ventricular hypertrophy. The criteria, which have been suggested in the past for such a diagnosis, refer almost exclusively to the fact that the ratio of the R to S wave in V_1 or V_{R3} is greater than one and to the persistence of an S wave in left-sided chest leads. They are of limited usefulness when applied toward the interpretation of precordial electrocardiograms of adults but are unreliable when applied to young children. The differentiation of electrocardiograms of right ventricular hypertrophy due to congenital heart disease from those frequently encountered in normal young children is of the utmost clinical importance. There is, however, no apparent, s i m p l e method of doing so by conventional electrocardiography.

A vectorcardiographic study of normal infants and children was conducted and compared with those obtained from children with congenital cardiac anomalies associated with right ventricular hypertrophy in order to contribute to the solution of this problem.

It was found that the spatial vectorcardiograms of normal young children could be distinguished without difficulty from those of children of the same age afflicted with congenital heart disease and right ventricular hypertrophy. The two vectorcardiograms did not differ merely by degree, but

there appeared to be a true qualitative difference between the normal and the abnormal.

Spatial vectorcardiography affords a simple means of distinguishing between different cardiac electromotive field forces, although they result in similar, almost identical electrocardiograms. It has been found well suited to routine application and certainly will prove to be a valuable clinical tool.

The theoretical basis of spatial vectorcardiography has been the subject of extensive investigations. A brief introductory discussion of it will only be entered into in this report. Other papers[6, 7, 8, 9] have dealt with the subject fully and it is to them that the reader is referred for greater details.

Spatial vectorcardiography is a method of recording the electromotive forces of the heart in several planes, e.g., the frontal, sagittal, and horizontal.

The activation of the heart is accompanied by the generation of an electrical field within the heart and the surrounding tissues. Since the discharge does not occur simultaneously throughout the heart, but in a regular sequence in different parts of the myocardium, the resultant balance of all the forces generated varies in magnitude, direction, and sense from moment to moment. At any one moment, this balance of forces may be represented by an instantaneous vector. The distal points of all the instantaneous vectors describe a loop during the period of excitation, which is referred to as a cardiac vector loop. The term spatial cardiac vector is used since the electromotive field thus represented extends into three dimensions. The records representing the projection of the spatial cardiac vector to preselected planes are referred to as spatial vectorcardiograms.

The value of unipolar leads lies in their ability to record the electromotive forces as they are found at any one point. The unipolar extremity, chest, and esophageal leads may be considered as representing the scalar projections of the spatial vectorcardiogram along a line drawn from the "exploring electrode" through the electrical center (E) of the heart.[7, 8] A positive deflection (R wave) is inscribed when the loop is on the proximal side of E; a negative deflection (Q or S wave) is recorded when the loop is on the distal side of E. The bipolar extremity leads of Einthoven represent the scalar projection of the spatial vectorcardiogram onto the sides of a triangle, the plane of which is determined by the right arm, left arm, and left leg.

The cardiac vector records the time course of the instantaneous electrical axes of the heart during depolarization and repolarization. Three bipolar leads are placed on the thorax as to form an x,y,z axis with the common point of origin at the right posterior axillary line just below the diaphragm. A cube thus formed will have the electrical center "E" at its center. These three bipolar leads are connected to three oscilloscopes so as to form a horizontal, sagittal, and frontal projection of the spatial cardiac vector and are photographed simultaneously. The Technicon cardiograph and vectorscope have been used throughout.

In the present report, the spatial vectorcardiograms of normal young children will be compared with those having right ventricular hypertrophy due to congenital heart disease.

MATERIAL AND METHODS

All vectorcardiograms were obtained from children in the clinics and wards of the Mount Sinai Hospital. The "normal" children were normal only in respect to cardiac function and size. This was determined by clinical examination and fluoroscopy. A small amount of sedation was administered to the younger children just prior to the recording of the vectorcardiogram.

The vectorcardiograms were obtained by the use of a Technicon electrocardiographic machine and vectorscope. The spatial vector or QRS sÊ loop was visualized and photographed as it projected onto the frontal, sagittal, and horizontal planes on three oscilloscopes simultaneously. The electron beam was interrupted 400 times per second by intensity modulation in order to permit a time analysis. Electrocardiograms were recorded, including unipolar leads around the chest.

Nine cases were selected as representative of the entire series of normal children studied.

RESULTS

Two were 8 months of age, three were 15 months old, one was 18 months old, one was 3½ years old, one was 5 years old, and one 8 years old. The horizontal, sagittal, and frontal plane projections appear in that order, reading from left to right. (Figs. 1, 2, 3,*A* and *B*.)

Inasmuch as we are chiefly concerned with an explanation of the tall R wave in lead V_1, most attention will be directed toward the horizontal plane projection. It is believed that the precordial leads are most intimately related to this projection of the spatial vector and that any precordial lead can be accurately predicted from it. The derivation of precordial leads proceeds along the same lines as the derivation of standard and unipolar extremity leads from the frontal projection of the vectorcardiogram.[8] Considerable difference of opinion exists as to the validity of the former relationship, but simple observation of the horizontal plane vector loops and the precordial electrocardiogram compels the conclusion that the concept has great usefulness even if a mathematically exact correlation does not exist. However, in a larger sense the observation that the spatial vectorcardiograms of normal children are different from those with right ventricular hypertrophy is valid in itself and any doubts as to the relationship between precordial leads and the horizontal plane vectorcardiogram cannot invalidate the original observation.

The vector loops in the frontal plane projection are narrow, run generally clockwise, and the long axes lie in the range of 0 and 90 degrees. This results in a normal axis deviation in all cases but Case 272, which is deviated furthest to the right and shows prominent S waves in the three standard leads.

The horizontal plane vectorcardiogram, in all cases, shows a large initial anterior loop which extends much more anterior than is seen with normal adults. This feature is characteristic of the young child's vector loop. It may be seen that this large initial anterior extension will produce an R wave of large amplitude in lead V_1 or V_2. The extent of this anterior arc is well seen in the sagittal plane projection. The loop continues to the left and downward, then turns in a coun-

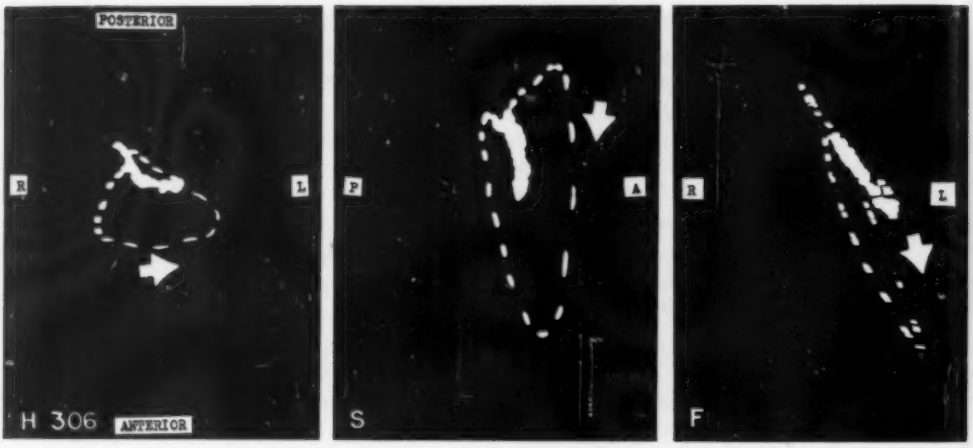

Fig. 1*A*.—Spatial vectorcardiogram, normal child, 8 months of age, horizontal (*H*), sagittal (*S*), and frontal (*F*) projection. The centrifugal (initial) limb of the QRS vector is oriented markedly anteriorly (*H* and *S*), but the centripetal limb returns posteriorly and counterclockwise in the horizontal projection. The T vector is oriented left lateral and inferior.

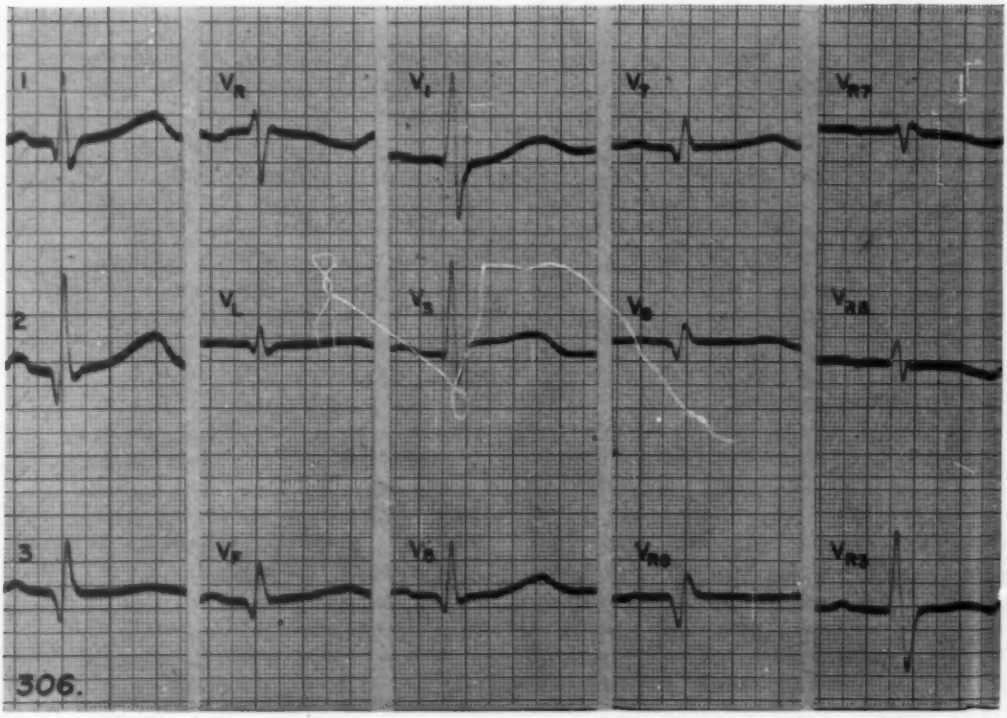

Fig. 1*B*.—The electrocardiogram (recorded at 10 cm. per second, i.e., four times conventional speed) shows R waves in leads V_1 and V_{R2} exceeding that of the S waves. The T waves are upright in the conventional chest leads.

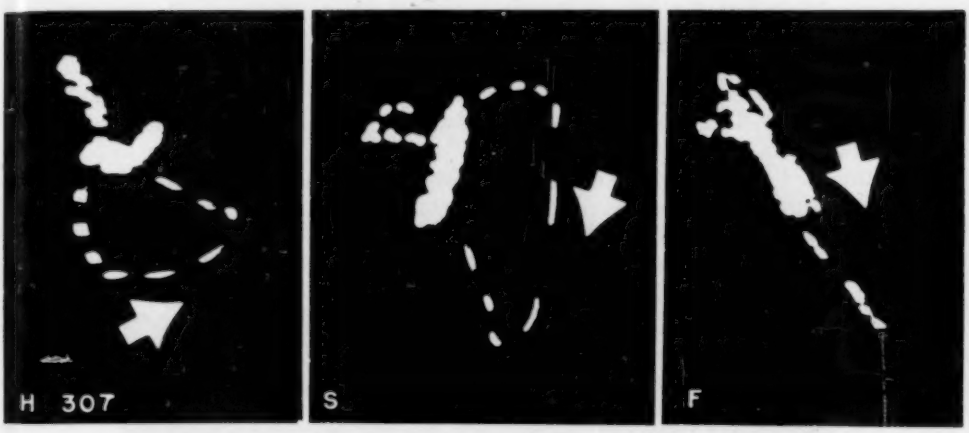

Fig. 2*A*.—Spatial vectorcardiogram, normal child 8 months of age. The general configuration and orientation of the QRS loop is similar to that in Fig. 1*A*. The T vector, however, is oriented somewhat more posteriorly. This will cause the T waves in right precordial leads to be inverted since the vector is located in the negative field of an exploring electrode V_1 and V_2.

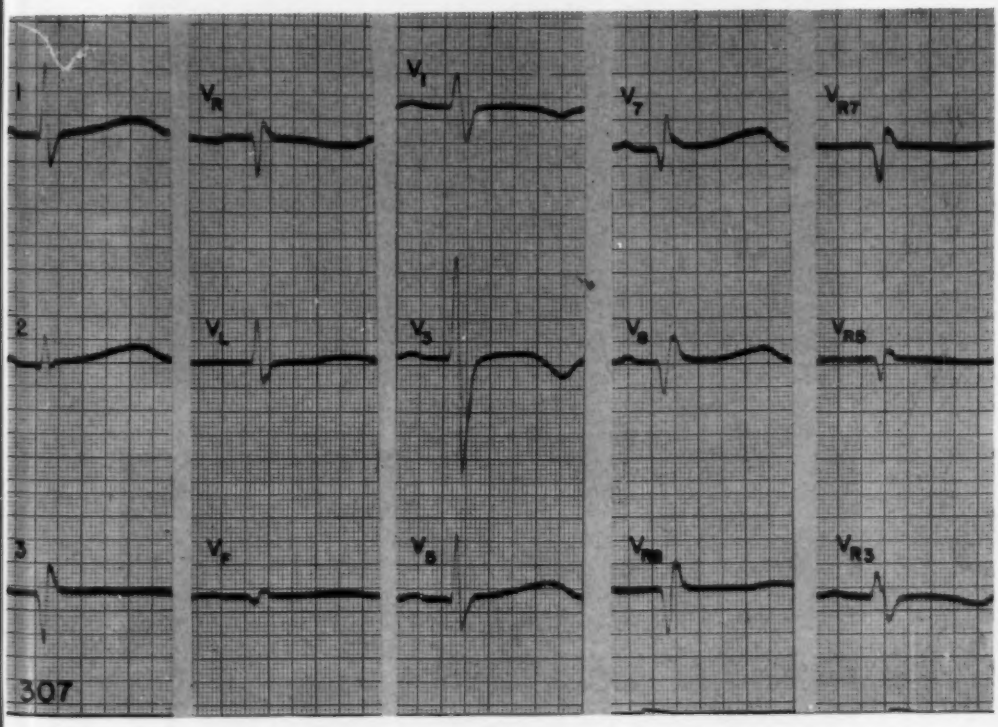

Fig. 2*B*.—The electrocardiogram (10 cm. per second) reveals equiphasic RS waves in V_{R3}, V_1, and V_2 with inverted T waves as was to be expected from the spatial vectorcardiogram.

terclockwise direction and the centripetal limb returns to the isoelectric center by proceeding posterior to the centrifugal limb. The loop, therefore, has its centrifugal limb in front and the centripetal limb behind. This rotation and relationship of centripetal to centrifugal limb is the same as that observed in normal adults.[8] The sole difference between the spatial vector-loop of adults and children is that the initial anterior arc is nearly always small in the adult, resulting in a small r wave in V_1, and large in the child, resulting in a large R wave in V_1. Since the bulk of the vector loop is posterior to the central plane in the adult, deep S waves are recorded in lead V_1. In the child, the bulk of the loop is anterior to the center and small

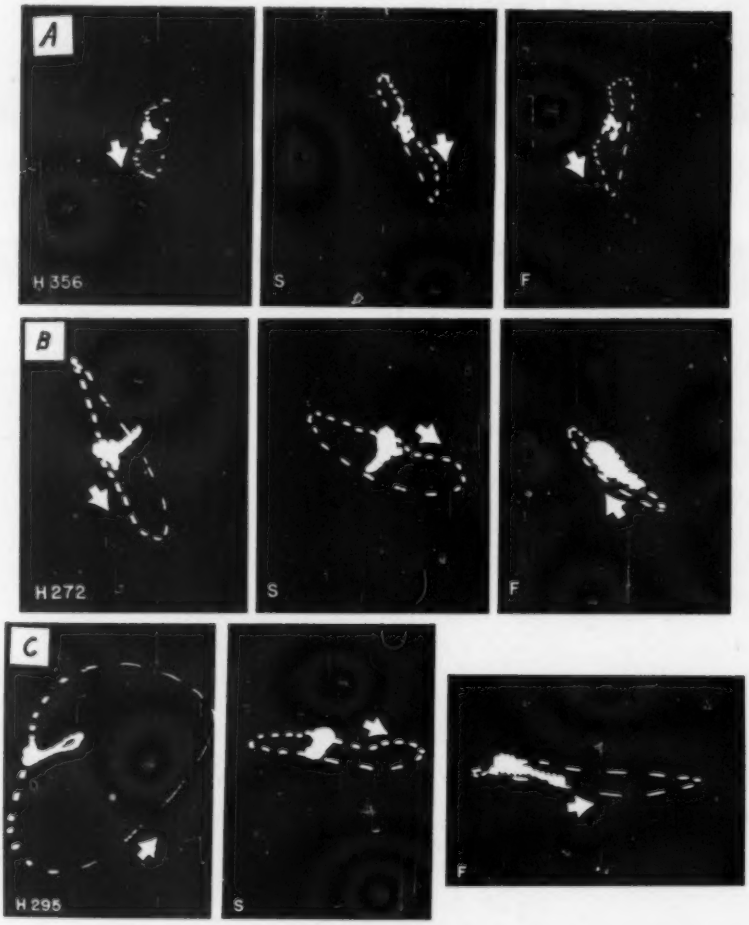

Fig. 3A.—Spatial vectorcardiograms of three normal children, 15 months of age. All three show a marked anterior position of the centrifugal, but a posterior return of the centripetal limb with counterclock rotation in the horizontal projection.

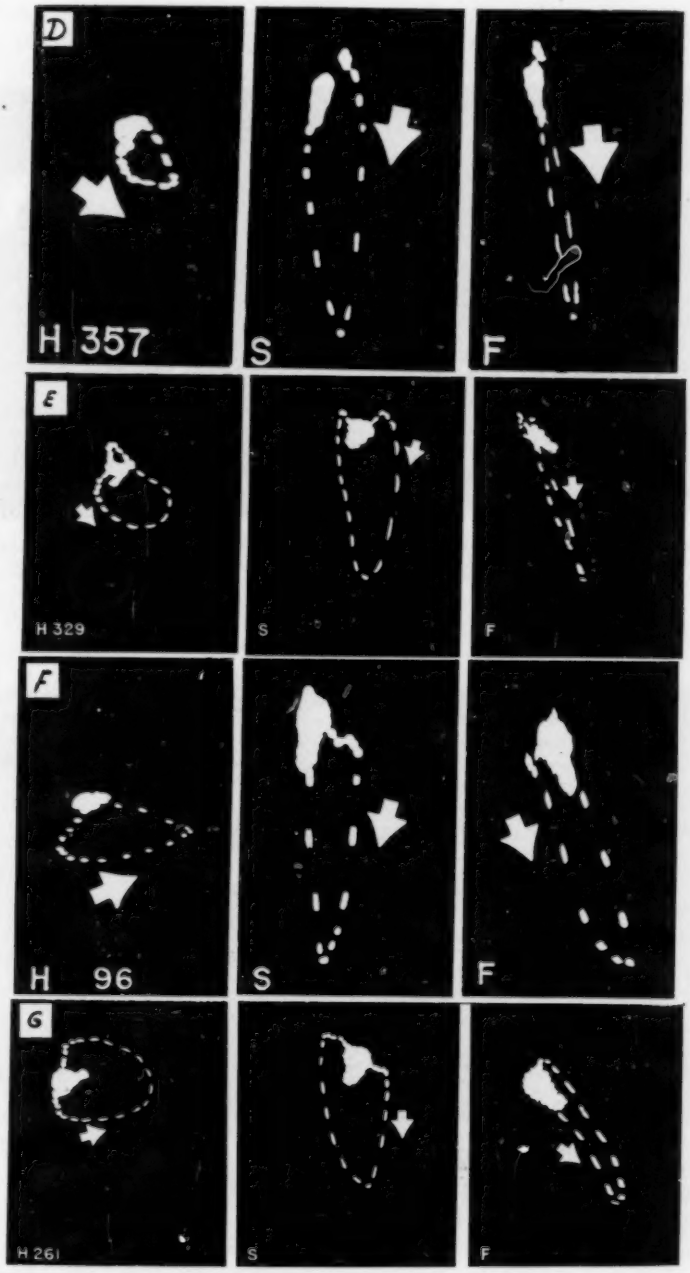

Fig. 3*B*.—Spatial vectorcardiograms of four normal children 18 months (*D*), 3½ years (*E*), 5 years (*F*), and 8 years (*G*).

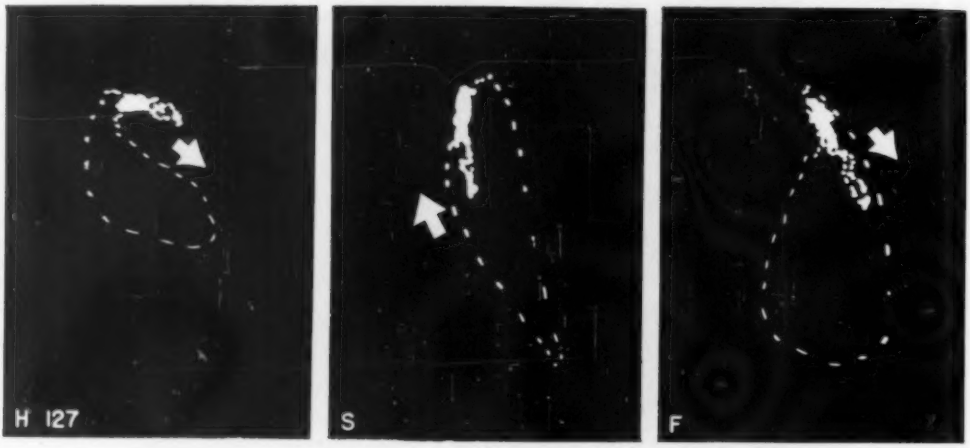

Fig. 4*A*.—Spatial vectorcardiogram of a 3-year-old child with interatrial septal defect and pulmonic stenosis. In the horizontal projection the centrifugal limb is similar to that found in normal children. The centripetal limb, however, returns anterior to it with clockwise rotational direction.

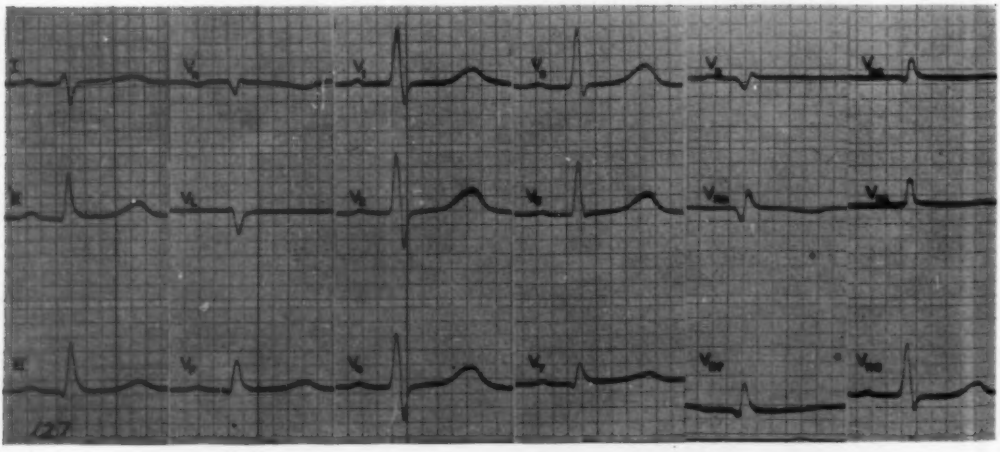

Fig. 4*B*.—The electrocardiogram (10 cm. per second) shows in precordial leads V_{R2}, V_1, and V_2 amplitudes of the R waves exceeding those of the S waves. Note the slight slurring of the upstroke of R in V_{R2} and V_1. Also note the similarity of these precordial leads to those shown in Fig. 1*B*.

s waves are often found in lead V_1. In general, the more anterior the position of the loop, the greater the value of the R/S ratio.

The vectorcardiogram seen in Fig. 4 is one obtained from a 3-year-old child with an interatrial septal defect and pulmonary stenosis. This pattern is the one found with right ventricular hypertrophy of a marked degree. They have all been described in detail previously.[9] The vast majority of children with congenital cardiac anomalies associated with right ventricular hypertrophy display vectorcardiograms resembling this or variations thereof. It is obvious that both of these spatial loops are vastly different from the normal children. The horizontal plane vectorcardiogram shows the difference most clearly. First, the normal direction of rotation is counterclockwise, whereas in right ventricular hypertrophy it is clockwise. Second, and most important, the centripetal limb of the loop lies anterior to the outgoing or centrifugal limb and this, too, is the reverse of the normal pattern. Third, the R wave of V_1 does not display a smooth upstroke in the patients with right ventricular hypertrophy. This can be reasoned from the vectorcardiogram which shows that a temporary reversal of polarity must occur at the V_1 electrode because of the sharp change in direction which the loop undergoes when the centripetal limb turns and runs anterior to the centrifugal one. The electrocardiogram reflects this clearly. The vectorcardiograms of the normal children show that the upstroke of the R wave of V_1 will be smooth.

The marked difference between the vectorcardiograms of the normal children and those of the children with right ventricular hypertrophy is apparent. For the reasons detailed above, it is believed that the vector pathway which results in a tall R wave in lead V_1 in normal children is so dissimilar to that of the children with right ventricular hypertrophy that different electrophysiologic events are responsible.

DISCUSSION

The data which have been presented indicate clearly that the vectorcardiograms of normal infants and young children are very different from those obtained in children of the same age with congenital cardiac anomalies and right ventricular hypertrophy. There should be no difficulty with their differentiation in the future.

The very earliest alterations of the vectorcardiogram which occur as a result of hypertrophy or dilatation of the right ventricle are not known. Nor are we aware of the possible influence of various patterns resulting from hypertrophy of localized areas such as the interventricular septum or the crista terminalis. Therefore, it is actually not possible to state whether the spatial vector of normal children is or is not a result of the relative degree of the right ventricular preponderance which is seen in the child as contrasted with the adult. What can be stated is that the electrical pattern of the normal child is distinctly different from that of the abnormal. Apparently, it is only in the first month of life that the ratio of right to left ventricular mass is similar to that found in congenital cardiac malformations. By the end of the second year, the left ventricle weighs twice as much as the right and is twice as thick.[10] The

main reason for believing that the right ventricular hypertrophy pattern is not merely an advanced degree of the normal is that the former affects the centripetal or secondary limb of the vectorcardiogram while the latter affects the centrifugal or initial portion.

SUMMARY AND CONCLUSIONS

1. The vectorcardiograms obtained in normal children below the age of 8 years have been compared with those of children of the same age who have right ventricular hypertrophy associated with congenital heart disease.

2. Inasmuch as both groups present similar electrocardiograms which display prominent R waves in lead V_1, the normal electrocardiogram cannot be distinguished from the abnormal with any certainty.

3. The spatial vectorcardiograms, however, of the normal children are found to be distinctive and readily distinguishable from those of the children with congenital heart disease.

a. The horizontal plane vectorcardiogram of the normal children is characterized by (1) a large initial anterior loop which is mostly counterclockwise in rotation, (2) inscription of the centripetal limb posterior to the centrifugal one, and (3) inscription of the majority of the loop anteriorly. This results in tall, smooth R waves and relatively small s waves in lead V_1.

b. The vectorcardiograms of children with congenital heart disease are characterized by a small initial loop, clockwise rotation, and inscription of the centripetal limb anterior to the centrifugal one.

4. The relationship between the horizontal plane projection of the cardiac vector, as obtained by the present technique, and the unipolar precordial leads is demonstrated.

REFERENCES

1. (a) Master, A. M., Dack, S., and Jaffe, H. L.: The Precordial Lead of the Electrocardiogram of Normal Children, Am. J. Dis. Child. 53: 1000, 1937.
(b) Richman, B., and Master, A. M.: The Unipolar Chest and Extremity Lead Electrocardiogram in Children (Newborn to Ten Years Old), Am. Heart J. 41: 687, 1951.
2. Battro, A., and Mendy, J. C.: Precordial Leads in Children, Arch. Int. Med. 78: 31, 1946.
3. Switzer, J. L., and Besoain, M.: Electrocardiograms of Normal Children, Am. J. Dis. Child. 79: 449, 1950.
4. Alimurung, M. M., Joseph, L. G., Nadas, A. S., and Massell, B. F.: The Unipolar Precordial Electrocardiogram in Normal Infants and Children, Proc. New England Cardiovascular Society, April 3, 1950, p. 49.
5. Tudburg, P. B., and Atkinson, D. W.: The Electrocardiograms of One Hundred Normal Infants and Young Children, J. PEDIAT. 36: 466, 1950.
6. Duchosal, P. W., and Sulzer, R.: La Vectocardiographie, Basel and New York, 1949, S. Karger.
7. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal, and Horizontal Projections, I. Am. Heart J. 41: 483, 1951.
8. Scherlis, L., Lasser, R. P., Grishman, A.: Spatial Vectorcardiography: The Normal Vectorcardiogram, VI., Am. Heart J., In press.
9. Lasser, R. P., Borun, E. R., and Grishman, A.: Spatial Vectorcardiography: Right Ventricular Hypertrophy as Seen in Congenital Heart Disease, VII., Am. Heart J., In press.
10. Scammon, R. E.: A Summary of the Anatomy of the Infant and Child, in Abt's Pediatrics, Philadelphia, W. B. Saunders Co., vol. 1, p. 394.

THE WEIGHT PROGRESS OF PREMATURE INFANTS GIVEN SUPPLEMENTARY FEEDINGS OF VITAMIN B_{12}

A Comparative Study

HENRY RASCOFF, M.D., ALLA DUNEWITZ, M.D., AND ROBERT NORTON, M.D.
BROOKLYN, N. Y.

THE encouraging report by Wetzel[1] on the use of vitamin B_{12} in combating malnutrition and slow growth in children and Lueck's[2] findings that animals given the vitamin gained more weight than a control group have aroused a great deal of interest in the profession as to its effect on other phases of growth and development. Accordingly, a study of the effect of vitamin B_{12} on the weight progress of premature infants was started at the Beth-El Hospital in May, 1950.

MATERIAL AND METHODS

A solution of crystalline vitamin B_{12} in distilled water,* with 1.5 per cent benzyl alcohol as a preservative, was used, each cubic centimeter containing 100 μg of the vitamin. The preparation was dispensed in a bottle with a calibrated dropper so that a drop contained about 5 μg of the B_{12}.

Each infant, 5 pounds or less, admitted to the premature nursery was given the preparation beginning on the fifth day of life. A drop containing 5 μg of the B_{12} solution was put into a small amount of formula and extra measures were taken by the nursing staff to be certain that the infant received the vitamin each day. This continued until the child was discharged from the premature nursery. In some instances the vitamin was given at home for a period of six months.

(The following routine is used in the premature nursery: Nothing by mouth for twelve to twenty-four hours. Sterile water is offered in dram quantities during the second twelve-hour period. During the second day, the infant is offered small but increasing amounts of an evaporated milk-Dextri-Maltose mixture in the proportion of one part of evaporated milk to two parts of water with 5 per cent Dextri-Maltose. The concentration is gradually increased and adjusted to the infant's growing needs. All of these newborn infants are given vitamin K by injection during the first twenty-four hours. On the fifth day, a suitable multivitamin preparation is given to supply the metabolic needs for vitamins A, B, complex, C, and D.)

The study was divided into two phases, (1) the weight progress of the infants during their hospital stay, and (2) the progress after discharge from the hospital and followed up at home for varying periods up to six months. At the time of discharge, the mother was given about a month's supply of the vitamin and directed as to dosage. If the newborn infant was a service case, the infant returned in a month for examination. An additional supply of the vitamin was given for further therapy. Those under

From the Pediatric Department, Beth-El Hospital.

*Supplied by Merck and Company, Rahway, N. J.

care of private physicians were similarly advised and the vitamin supplied by their own doctor.

The Beth-El Hospital is a voluntary institution and serves largely a lower middle and working class group. A majority of the patients are delivered and cared for by private physicians. All the doctors called upon cooperated willingly by mailing in monthly reports on printed post cards previously furnished for that purpose. The service cases were followed in the clinic by one of us (A. D.).

Table I. Weight Progress of Premature Infants Receiving Vitamin B_{12} Supplement as Compared to a Group Not Receiving the Vitamin

BIRTH WEIGHT (GM.)	NO. CASES	M	F	AV. BIRTH WEIGHT (GM.)	AV. DAYS RETURN TO BIRTH WEIGHT	AV. DAYS IN HOSPITAL	AV. WEIGHT GAIN (GM.) PER DAY 7-28 DAY OF LIFE
1,000 to 1,500	5	3	2	1,350.9	9.8	47.8	22.8
	28	*12*	*16*	*1,366.5*	*9.9*	*50.7*	*23.6*
1,501 to 2,000	19	7	12	1,835.4	11.0	27.5	25.8
	149	*69*	*80*	*1,803.0*	*8.3*	*32.2*	*26.1*
2,001 to 2,500	16	9	7	2,143.2*	5.6*	15.1*	25.8
	680	*310*	*370*	*2,319.0*	*5.1*	*11.5*	*26.4*

The italic numbers represent a comparative report,[2] previously published from this institution, of the hospital progress of 857 premature infants similarly treated but not given vitamin B_{12}.

*The apparent difference in the average birth weight and days in the hospital between the two groups is due to a slight variance in the procedure of both studies. In the vitamin B_{12} series only those infants weighing less than 2,280 grams and cared for in the premature nursery were included in this group. The larger control series included all infants born at the Beth-El Hospital weighing less than 2,508 grams.

Table II. A Comparative Study of the Average Daily Weight Gain by Birth Weight Groups (Grams)

BIRTH WEIGHT	NO. CASES	0-2 MO.	2-4 MO.	4-6 MO.
1,000 to 1,500	5	23.6	21.5	25.3
	16	*10.5*	*23.5*	*26.5*
1,500 to 2,000	6	30.6	25.4	21.6
	94	*14.5*	*29.4*	*21.5*
2,01 and over	29	30.7	28.0	20.1
	49	*14.8*	*30.0*	*24.7*

The italic numbers represent a group of premature infants treated at the Cook County Premature and Outpatient Department.

WEIGHT PROGRESS OF THE PREMATURE INFANTS WHILE IN THE HOSPITAL

Eighty-two infants of this group were originally started on the vitamin therapy. Forty-two were eliminated from the final tabulation because they were either fed other types of formulas, developed some illness, or could not otherwise be studied adequately. The hospital stay of these infants ranged from eight to fifty-eight days, and the total individual amount of the vitamin given varied from 15 to 290 μg.

For a statistical and comparative study, the cases were divided into three weight groups and the results compared with a similar but much larger study[3] previously done in this hospital of infants who had received a like dietary but not the vitamin B_{12} (Table I). It will be noted that there is but a slight difference in the average daily weight gain between the group receiving the B_{12} and the

control group. Actually, the infants not receiving the added vitamin showed a slightly better daily gain.

WEIGHT PROGRESS OF INFANTS AFTER DISCHARGE FROM THE HOSPITAL

Forty-one premature infants born at the Beth-El Hospital were followed up at home, while on daily doses of 5 μg of vitamin B_{12}, for periods varying from two to six months. The weight progress was compared to a follow-up study of infants treated at the Cook County Children's Premature Station and Outpatient Department.[4] The recorded small gains in the first two months of the Chicago infants were attributed by Glaser and associates to the regime followed in the hospital. The diet was rigidly controlled. It was probably calorically below the amount which most of these babies would have been able to take as demonstrated by the rapid increase of food intake after discharge from the hospital. The increased weight gain of these infants in the next four months made up for the initial inferior performance as compared to the Beth-El group.

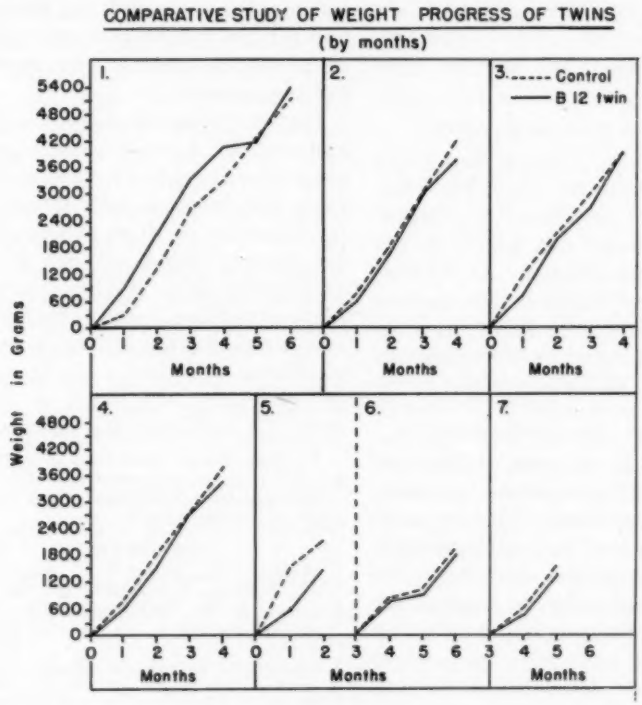

Fig. 1.

TWINS USED AS PART OF A CONTROL STUDY

Seven sets of twins were used as part of our study to determine the possible beneficial effect of vitamin B_{12} on the weight pattern. The smaller of the twin in each instance was given 5 μg daily (twin No. 3 was

given 10 μg) for periods of from two to six months. The larger of the two was used as a control. In only one instance was the smaller one able to reach or surpass the weight of the larger sibling (Fig. 1).

RESPONSE TO QUERY ON APPETITE

One hundred twenty-five post-card replies were tabulated as to the question of the infant's appetite while receiving the B_{12}. Forty-nine were reported as "excellent," sixty-four as "good," ten only "fair," and two answered that the appetite was "poor."

EFFECT OF INCREASED DOSAGE

Eight premature infants were given 10 μg of vitamin B_{12} daily, but when no apparent advantage was noted after two weeks, this phase of the study was discontinued. At present, the premature infants under observation are receiving 20 μg of the vitamin daily. A report of this study will be furnished at its completion.

SUMMARY AND CONCLUSIONS

1. The weight progress of forty infants given daily supplementary feedings of 5 μg of vitamin B_{12} were studied and compared with a larger similar group which did not receive the vitamin. There was no appreciable difference in the weight gain of either group.

2. Forty-one premature infants born at the Beth-El Hospital were followed up at home for varying periods of from two to six months, during which time they received 5 μg of the vitamin daily. Their weight progress in the first two months was good when compared to a group from the Cook County Hospital not receiving the vitamin. However, one must consider the restricted regime followed at the latter hospital while these infants were in the premature nursery.

3. The appetite was indicated as "excellent" or "good" in over 91 per cent of the replies received.

4. The weight progress of seven sets of twins, the smaller of which received the vitamin daily, was studied. In only one instance was the smaller sibling able to reach or surpass the weight of the larger twin.

5. Premature infants given 5 μg of vitamin B_{12} daily did not show any appreciable weight gain over groups of premature infants not receiving the preparation.

During the period of study a report appeared in *Science*[5] describing the progress of twenty-five premature infants who received daily intramuscular injections of 10 μg of vitamin B_{12} for varying periods of from three to twenty-two days. When compared to twenty-three control patients, it was noted that the difference was insignificant. In fact, a slight margin of superiority was noted in the infants not receiving the vitamin.

Dr. Bela Schick, Consultant in Pediatrics, Beth-El Hospital, suggested this study.

The assistance of Helen Fine, R.N., is gratefully acknowledged.

REFERENCES

1. Wetzel, N. G., Fargo, N. C., Smith, I. H., and Helikson, J.: Science **110:** 651, 1949.
2. Lueck, R. W., McMillen, W. N., Thorp, F., and Boniece, J. R.: Science **110:** 139, 1949.
3. Gruber, S., Litvak, A., Rascoff, H., and Norton, R.: J. PEDIAT. **35:** 70, 1949.
4. Glaser, K., Parmelee, A., and Plattner, E. Pediatrics **5:** 132, 1949.
5. Downing, D. F.: Science **112:** 181, 1950.

Addendum

Twenty-five additional premature infants were given supplementary feedings of 20 μg of vitamin B_{12} daily for varying periods up to two months. There was no remarkable difference in the weight progress of these infants as compared to the previous group of control patients.

POLYARTERITIS NODOSA IN INFANCY AND CHILDHOOD

DONALD B. FAGER, M.D., JOHN A. BIGLER, M.D., AND JAMES P. SIMONDS, M.D.
CHICAGO, ILL.

IN 1866, Kussmaul and Maier[1] first accurately described a definite inflammatory disease of the medium and small arteries and called the condition "periarteritis nodosa." It is claimed that the disease was recognized as early as 1755 by Michaelis and Matani.[2] In 1810, Pelletan[3] reported a case in which numerous small aneurysms were present. In 1852, Rokitansky[4] described the macroscopic lesions of the disease in a young man who had died with symptoms of dysentery in whom he found innumerable aneurysms in the wall of small arteries over the entire body with the exception of the brain. In 1877, Eppinger[5] confirmed the diagnosis by studying the microscopic sections of that case.

The literature has been well summarized by several authors—Schreiber (1904),[6] Lamb (1914),[7] Ophüls (1923),[8] Gruber (1926),[9] and Rothstein and Welt (1933).[10] Rothstein's summary of the world literature brought the total number of cases to 195. He found the disease to be four times as frequent in males as in females. Up to that time it had been found to occur between the ages of 3 months and 78 years. About half occurred during the third and fourth decades of life and only twenty-three cases had been reported in infancy and childhood up to the age limit of 15 years. The percentage incidence was then 11.8 during childhood. Of the twenty-three cases in infancy and childhood, two occurred during the first year of life, four between the third and seventh years, and seventeen between the tenth and fifteenth years. These occurred in a ratio of 1.6 males to one female in contradistinction to the figures of four males to one female given for the disease in general.

A review of the English literature since the first description of polyarteritis nodosa reveals a total of 484 cases. These range in age from 10 days to 89 years. In the adult group (those above the age of 15 years), the disease occurs in the ratio of 2.3 males to one female. As shown in Table II, the fourth decade has the highest incidence.

Only fifty-two cases have been reported in the English literature in infancy and childhood up to the age limit of 15 years. The percentage incidence is 10.7 during childhood. Of the fifty-two cases in infancy and childhood, eight cases occurred in infancy (under 2 years of age), seventeen between the ages of 2 and 8 years, and twenty-seven between the ages of 9 and 15 years. In this group the disease occurs in the ratio of 1.08 females to one male in contrast to the adult ratio of 2.3 males to one female.

From The Children's Memorial Hospital and the Otho S. A. Sprague Laboratories.

TABLE I. AUTHORS OF CASES IN THE ENGLISH LITERATURE OCCURRING IN INFANCY AND CHILDHOOD

AUTHOR	YEAR	AGE*	SEX
Dickson[11]	1908	14½	M
Lamb[7]	1914	10	F
Wordley[12]	1923	13	M
Gray[13]	1926	12	M
Rothstein and Welt[10]	1933	7	M
	1933	10	M
Barnard and Burbury[14]	1934	8	F
Neale and Whitfield[15]	1934	15	M
Friedberg and Gross[16]	1934	7½	M
	1934	10	F
Krahulik, Rosenthal, and Loughlin[17]	1935	9	F
Dunbar[18]	1936	15	F
Spiegel[19]	1936	6	M
	1936	8	M
	1936	10	F
	1936	10	F
	1936	7	M
	1936	10	M
Vining[20]	1938	7	F
Hoyne and Steiner[21]	1940	8	M
Grant[22]	1940	12	M
Keeth and Baggenstoss[23]	1941	14½	M
	1941	3½	F
Maxwell and Maxson[24]	1941	10	F
Coe, Reisman, and De Hoff[25]	1941	9	M
Stewart[26]	1941	5	F
Goldman, Dickens, and Schenken[27]	1942	6	F
Rich[28]	1942	21 mo.	F
Jones, Jr.[29]	1942	15	F
Malamud[30]	1944	5	F
Scott and Potondo[31]	1944	5	F
	1944	9 mo.	F
Wilmer[32]	1945	25 da.	F
	1945	10 da.	M
Logue and Mullins[33]	1946	15	M
Diaz-Rivera and Miller[34]	1946	9 mo.	F
	1946	5	F
Day and Hesser[35]	1946	11	M
Peale, Gildersleeve, and Lucchesi[36]	1946	11	M
Miller and Daley[37]	1946	14	M
Pickard, Owen, and Dammin[38]	1947	15 mo.	F
Bradley[39]	1947	10	M
Fisher and Howard[40]	1948	13	F
Neale[41]	1949	9	F
	1949	8	M
Sinclar, Jr., and Nitsch[42]	1949	9 mo.	F
Klein[43]	1949	15	F
Taylor and Jacoby[44]	1949	7	F
Prouty and Schafer[45]	1950	9	M
Gemson[46]	1950	11	M
Present report	1950	4 mo.	M
	1950	6½	F

*Indicates age in years unless otherwise specified.

TABLE II. AGE DISTRIBUTION BY DECADES IN 421 PATIENTS WITH POLYARTERITIS NODOSA

AGE GROUP (BY YEARS)	PER CENT*
1 to 10	6.8
11 to 20	9.2
21 to 30	16.6
31 to 40	22.5
41 to 50	18.0
51 to 60	15.4
61 to 70	9.0
71 to 80	1.6
81 to 90	0.5

*Per cent to nearest tenth.

ETIOLOGY

From a review of the literature no one single agent has been found to be responsible for the production of polyarteritis nodosa. From the clinical and experimental work of Rich and Gregory,[47] it would seem that hypersensitivity is an important factor. They state that "the demonstration that periarteritis nodosa is a manifestation of anaphylactic hypersensitivity is in line with the long recognized fact that the blood vessels are susceptible to anaphylactic injury." They also demonstrated that marked lesions of the vessels can result from a single large injection of foreign serum in a previously nonsensitized body and that repeated injections after hypersensitivity has developed are not necessary for the production of vascular lesions. It would seem that hypersensitivity to some agent is the underlying cause for the development of disease.

In the two cases presented here the illness began with an infection. In one the diagnosis was viral pneumonia; in the other, scarlet fever. A sulfonamide was used in the first case and was not started until after the symptoms of polyarteritis were present.

It seems most likely that hypersensitivity plays an important role in the etiology and that the sensitivity may be related to the products of infection, bacteria, virus, or any other antigenic substance.

PATHOLOGY

The pathology, as described by Arkin,[48] is divided into four stages according to the changes present in the arteries. These are (1) alterative-degenerative, or beginning stage; (2) acute inflammatory stage; (3) granulation tissue stage, and (4) healed end-stage, or scar tissue stage.

The beginning stage is characterized by alterative-degenerative changes in the media with edema and the appearance of a thready fibrinous exudate about the elastica interna. There is swelling of the muscle cells with separation by the exudate. In the smaller arterioles, those without vasa vasorum, the changes are chiefly in the innermost media, in the subendothelium. In the larger arteries, those with vasa vasorum, the changes appear more often in the outer media, lying near the elastica externa. In either case part of or the entire circumference of the vessel wall undergoes a coagulative necrosis with a hyalin-like appearance. Leucocytes begin to wander into the necrotic area. They are chiefly polymorphonuclear leucocytes, though eosinophiles may also be present in considerable numbers. In this stage the adventitia is often unaffected.

The acute inflammatory stage becomes exudative. Great numbers of polymorphonuclear leucocytes and at times many eosinophiles, lymphocytes, and plasma cells take part in the lesions. The fibrinous exudate extends

into the intima and outward into the adventitia. The muscle cells of the media become separated from one another and then undergo complete necrosis; the elastic layers become fragmented and, although they survive longer than the muscle cells, soon disappear also. The perivascular connective tissue becomes edematous and leucocytes appear in large numbers. The fibrin threads of the exudate may penetrate into the lumen of the vessel and permit leucocytes to wander into the subendothelial tissue. A subendothelial connective tissue proliferation takes place—a reactive intima proliferation In this stage thrombosis of the lumen with infaretion is common. Aneurysm formation or rupture of the vessel wall with hemorrhage into the adventitia or surrounding tissue may occur. There is no suppuration.

The granulation tissue stage is a reparative process. There is active proliferation of fibroblasts from the adventitia into the inflammatory zone, accompanied by a reduction in the polymorphonuclear leucocytes with an increase in the lymphocytes and plasma cells. The fibrin network and hyalinized necrotic media are gradually replaced by cellular granulation tissue, rich in fibroblasts and newly formed blood capillaries. This tissue not only invades the subendothelial tissue through defects in the elastica interna but even invades the thrombus formed in the lumen. There is also a very marked reactive intima proliferation with a partial or total occlusion of the lumen. This proliferation is usually thickest at the site of the lesion with resultant narrowing of the lumen, which becomes excentrically placed.

The healed end-stage, or scar tissue stage, is characterized by replaced granulation tissue by an indifferent fibrous scar tissue poor in nuclei. The arteries become embedded in thick sheaths of scar tissue radiating through the affected organ. Where the arterial destruction was greatest there the periarterial healed granulation tissue is the thickest.

SYMPTOMS

Recognition of polyarteritis nodosa during life is very difficult because it so rarely starts as an initial disease entity. Not infrequently it follows some antecedent infection. In such instances there may be recovery from the antecedent infection and after a variable period symptoms of illness recur or the expected recovery of the antecedent infection does not take place and illness continues.

If there is any pattern of the symptoms it is of multiple organ involvement. Because of the multiplicity of organ involvement there may be symptoms relating to the heart, kidneys, lungs, central nervous system, muscles, joints, gastrointestinal tract, skin, and blood vessels. Cardiac murmurs are rarely present although there may be cardiac enlargement and even decompensation. Kidney involvement may manifest itself by hypertension, edema, and urinary findings. There may be abdominal pain and gastrointestinal bleeding. Convulsions and signs of meningeal irritation may be present. Symptoms or x-ray evidence of pulmonary disease may occur. Joint and muscle pains are not uncommon. Purpura and macular rashes may come and go. There is usually pallor and loss of weight.

Prolonged or intermittant fever is common. Pathognomonic is the palpation of subcutaneous nodules along the course of the subcutaneous blood vessels. A biopsy of such a nodule will lead to the correct diagnosis. It is uncommon in children to make a diagnosis from a biopsy of muscle or other tissue taken at random when a nodule is not present. Other than by biopsy of a nodule the laboratory findings are not characteristic other than the revealing of multiple organ involvement. Blood cultures are negative. There is some anemia and the leucocyte count is usually fairly high, being from 10,000 to 20,000 or more. An eosinophilia of 5 per cent or more may be present. The urine at some time will often give evidence of kidney involvement.

The duration of the disease may be from weeks to years. Recovery has been reported. The prognosis will depend upon the extent of organ involvement as well as upon the continuous progression of new blood vessel lesions.

Treatment has been far from satisfactory. The only therapy that has shown any evidence of success has been cortisone and ACTH. Carey and associates[49] have reported on the treatment of one patient and on the experiences of others. They showed by serial muscle biopsy during therapy that there was healing of the vascular lesions. But such lesions that have already progressed to the point of occlusion may still cause infarction during the healing process leading to death during therapy. Such therapy holds much promise but may depend upon the stage at which it is started. It also lends support to the hypersensitivity theory as the causative factor.

CASE REPORTS

CASE 1.—S. W., a 4-month-old white male infant, entered The Children's Memorial Hospital on June 29, 1949, with a history of daily fever since recovering from virus pneumonia one month prior to admission. He was born at full term following a normal spontaneous delivery and weighed 6 pounds. The neonatal period was uneventful. He gained and developed normally on an artificial milk formula. No history of previous disease or immunization was elicited. The family history was noncontributory.

The infant's illness began May 27, 1949, with high fever, cough, and rapid, labored breathing with slight cyanosis. He was hospitalized elsewhere the following day with the presumptive diagnosis of virus pneumonia. The white and differential counts were essentially normal. The red blood count was 2.5 million and the hemoglobin was 50 per cent. X-rays of the chest were interpreted as showing some minor evidences of infiltration compatible with a presumptive clinical diagnosis of virus pneumonia.

Treatment consisted of penicillin, aureomycin, oxygen, and parenteral fluids. During the next eight or nine days his temperature fell from 105° to 100° F. It was thought that he was making a satisfactory recovery. His temperature returned, however, to 102° F. and remained around that level for three weeks.

He was irritable when handled and favored resting on his back with his head turned to the left. This was said to have been characteristic of the infant since birth. On June 19, 1949, the penicillin and aureomycin were stopped but the fever remained.

During the next ten days the following diagnostic procedures were done: two blood and spinal fluid cultures were negative; a stool culture revealed no pathogens. Typhoid, paratyphoid, and Weil-Felix agglutinations were negative. A spinal tap done on June 20 was grossly bloody,

but on a repeat tap done on June 27 the fluid was clear with three white blood cells per cubic millimeter and a protein of 56 mg. per cent. Subdural taps revealed a few drops of clear fluid on both sides. Skull films were interpreted as within normal limits. A repeat chest film on June 26 showed no evidence of pulmonary pathology but the cardiac silhouette appeared somewhat larger than on earlier films. During the next ten days the white count, which had previously been within normal limits, increased progressively to 32,000 with a marked shift to the left without abnormal forms. The urine showed a faint trace of albumin and an occasional white blood cell.

A few days prior to admission the infant seemed to open his right upper eyelid less than the left. The corner of the mouth on the right side showed a suggestion of weakness, and the knee jerk on the left had become less active than on the right. His cry became higher pitched and more shrill than before, and his general condition seemed much less good than on several days previously. It was thought there might be some intracerebral pathology, and in view of this sulfonamides and streptomycin therapy were started.

On admission the physical examination revealed a normally developed, fairly well-nourished, moderately dehydrated 4-month-old infant who cried on the least provocation or when handled. His admission temperature was 104° F. The respirations were from 70 to 80 and the pulse was 160. Aside from slight asymmetry of the skull, thought to be due to the infant's assumed position, the physical examination was essentially normal.

The hemoglobin was 7.8 Gm. per cent; the red blood count was 3.44 million; the white blood count was 40,800. By differential count there were 86 per cent polymorphonuclear leucocytes, 13 per cent lymphocytes, and 1 per cent eosinophiles. Some cells were very hypochromic; a few were polychromic. There was moderate anisocytosis and some toxic granules. The urine pH was 5.5; the albumin was 2 plus, with one to two white blood cells per high-power field and a few hyalin casts. The blood nonprotein nitrogen was 36 mg. per cent. The sedimentation rate revealed a 33 mm. fall in one hour. Agglutinations against typhoid, paratyphoid, Brucella, and Proteus OX19 were negative. Blood cultures revealed no growth, and stool cultures no intestinal pathogens.

An x-ray of the chest revealed 25 per cent cardiac enlargement. The vascular shadows were slightly prominent below both hila. The lung fields were clear.

The electrocardiogram revealed sinus tachycardia, right axis shift, and a definitely abnormal record compatible with congenital heart disease.

During the terminal four days the infant's temperature gradually returned to normal. Anorexia, with dehydration, developed, and parenteral fluids and whole blood were administered. The hemoglobin increased to 13.1 Gm. per cent, the red blood cells to 5.4 million, and the white blood count remained elevated at 32,000 cells per cubic millimeter. The differential count revealed 63 per cent polymorphonuclear leucocytes, 23 per cent lymphocytes, 6 per cent monocytes, 8 per cent stabs, and 3 per cent normoblasts. Moderate toxic granulations were noted.

During the second hospital day, his color became dusky, and the respirations continued to be rapid. While awake, the respirations were slower and grunting. He became very apprehensive, and the cry was high pitched. The heart rate continued to be rapid but regular; the tones became less clear; however, no murmur was heard. The liver became palpable one inch below the right costal margin. The chest remained clear to auscultation. No localizing cerebral signs were elicited at any time. The clinical impression was that of a myo-

carditis with decompensation. He was placed in oxygen and started on digitalis and aureomycin.

On the fourth and final hospital day, cyanosis, restlessness, and grunting respirations were marked. Definite bronchial breathing was noted over the upper half of the left chest posteriorly. No definite dullness was noted and râles were absent. Pitting edema appeared over the lower extremities at this time.

At autopsy the external examination was essentially normal except for the tips of the right great and second toes which were dark purple-red in color and thought to be gangrenous. The abdominal cavity contained about 30 c.c. of clear straw-colored fluid. The anterior margin of the liver was 4 cm. below the xiphoid process in the midline and an equal distance below the right costal margin in the midclavicular line. It was one and seven-tenths heavier than normal weight for this age infant. The cut surface revealed marked congestion. The spleen projected 1½ cm. below the left costal margin in the anterior axillary line. Each pleural cavity had a smooth lining and contained 10 c.c. of clear, straw-colored fluid. The major gross pathology was in the heart, kidneys, and spleen.

The heart, opened and emptied of blood, weighed 64 grams (normal weight for this age is 27 grams). The apex was made up entirely of the left ventricle. Along the course of all of the coronary arteries were firm, raised, irregular, cordlike masses. All of the heart valves were normal. In the auricular appendage of the left atrium there was an adherent, somewhat dry, mottled, reddish-gray mass. The remainder of the endocardial surface was normal. The myocardium was a pale, grayish red and flabby. Behind the two anterior aortic cusps a small blunt probe could be introduced into the two coronary ostia and passed easily along the course of the vessels for a distance of 3½ cm. On transverse section of these arteries, 1 mm. irregular and eccentric lumens were surrounded by wide mottled red-gray masses which in their greatest diameters measured 8 to 9 mm. Similar changes were found along the course of their branches.

Each kidney was twice normal weight for this age infant and was similar in appearance. The capsules stripped easily, leaving a lobulated surface. Many of the lobules were reddish-gray while others were either in part or wholly pale yellowish-white in color and slightly elevated. On the left kidney there were more than a dozen yellowish-white areas, ranging up to 9 to 12 mm. in size. On cut surface the yellow-white areas extended into the cortex as rectangular and somewhat roughly triangular pale areas. The left renal artery was enlarged, firm, and a cordlike mass. On cut surface it was similar in all respects to the coronary vessels.

The spleen was normal in weight. Its lower third was adherent to the abdominal peritoneum and to the splenic flexure of the colon by grayish adhesions. The color of the spleen at this site was yellowish-red, as distinguished from the adjacent uniform dark red. On cut surface this lower portion was made up of sharply circumscribed, irregular, yellowish-white, structureless masses. The cut surfaces of the remainder of the spleen were purple-red with indistinct splenic corpuscles.

Microscopic sections of the coronary arteries, vessels of the kidney, spleen, and adrenal gland revealed the typical lesions of polyarteritis nodosa as originally described by Kussmaul and Maier[1] and more recently by Arkin.[48] The proximal portions of the coronary and renal arteries showed changes described by Arkin[48] as the acute inflammatory and granulation tissue stages. The vessels showed aneurysmal dilatation of their walls and partial occlusion of their lumens by thrombotic material with resultant excentrically placed lumens with absent endothelial

Fig. 1 (Case 1).—Heart showing the aneurysmal dilatation of a coronary artery and its raised, irregular cordlike form.

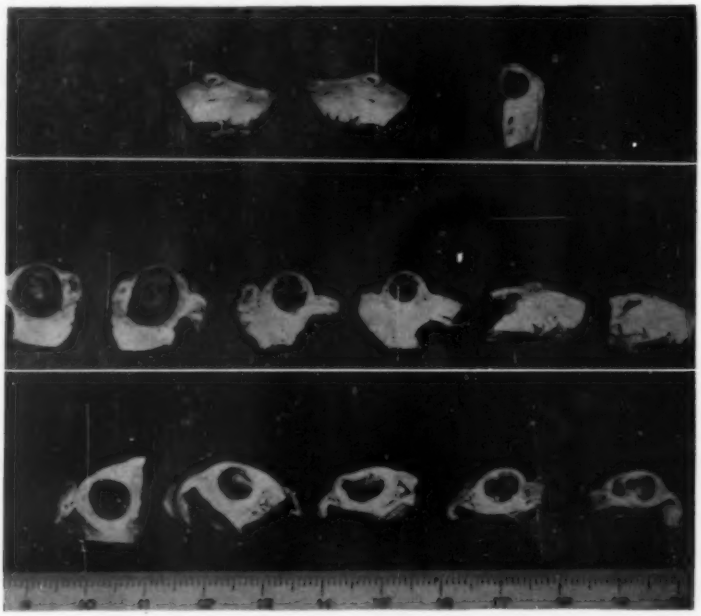

Fig. 2 (Case 1).—Serial cut surfaces of the right posterior descending, left circumflex, left anterior descending, and right coronary arteries, respectively.

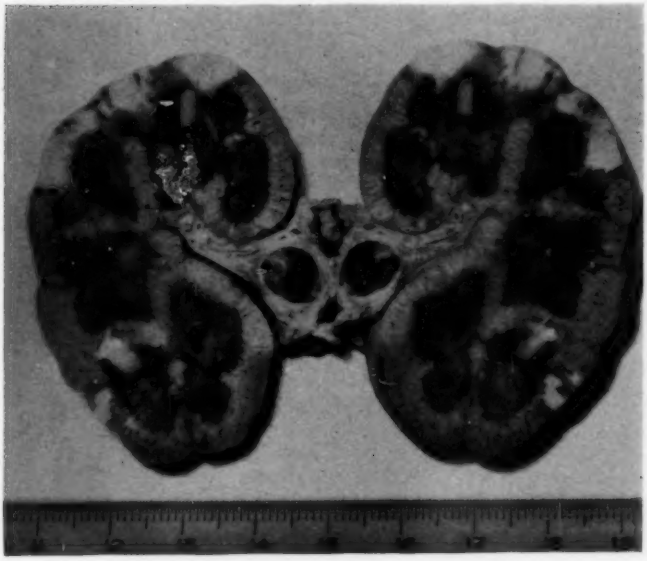

Fig. 3 (Case 1).—Kidney showing the aneurysmal dilatation of the splenic artery and numerous pale infarcts.

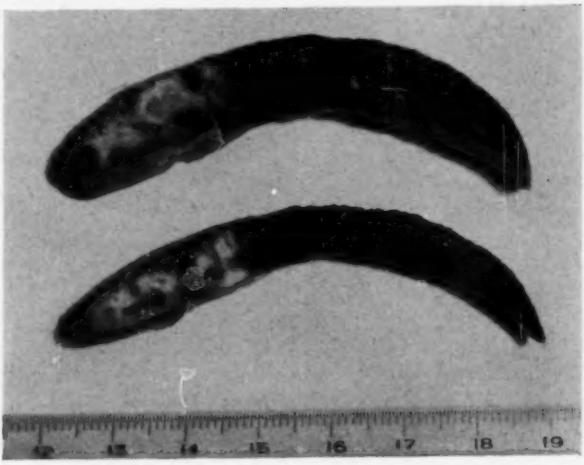

Fig. 4 (Case 1).—Spleen showing several irregular pale infarcts.

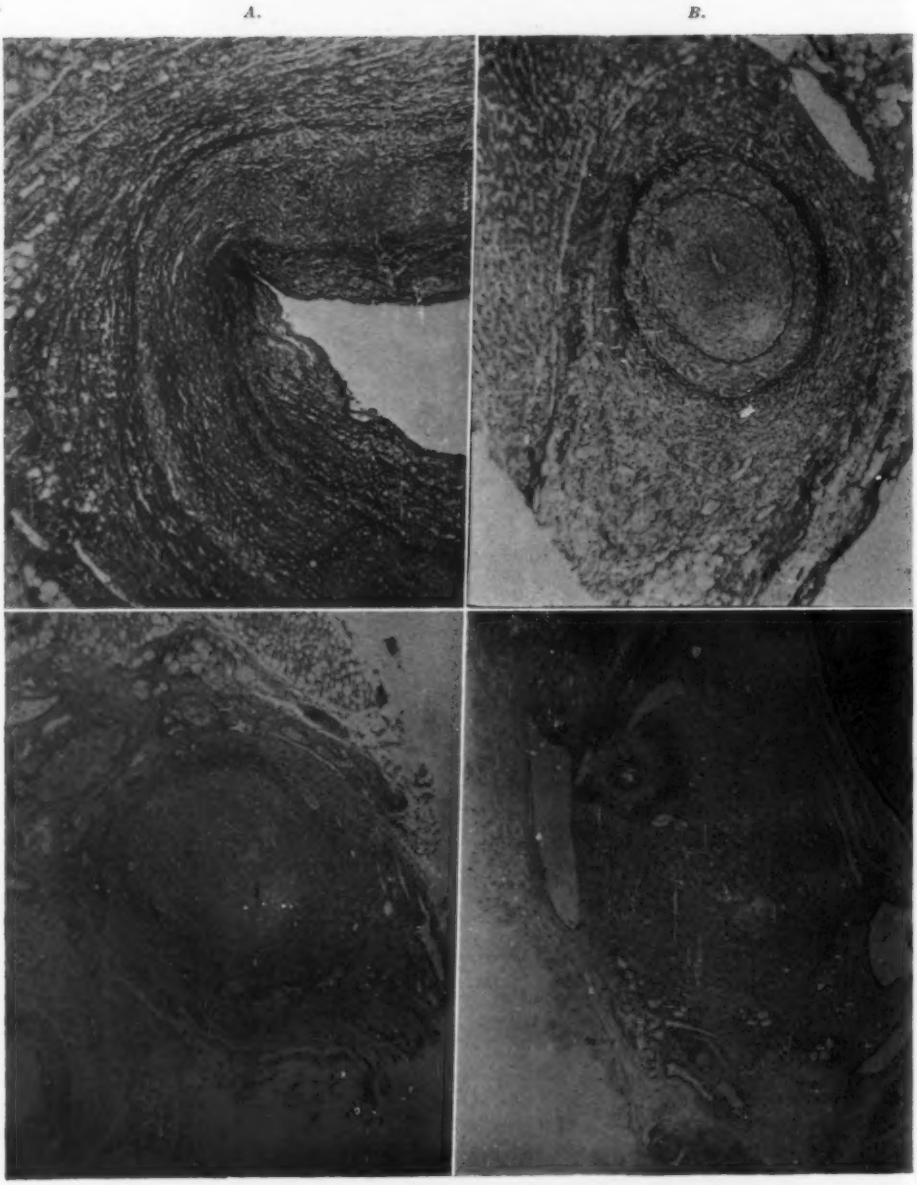

Fig. 5 (Case 1).—Typical arterial lesions found in polyarteritis nodosa. *A*, Coronary artery; *B*, kidney; *C*, spleen, and *D*, adrenal gland.

linings. The periphery of some thrombotic masses revealed invasion by endothelial buds and fibroblasts. The muscular coats were necrotic, irregular in thickness, edematous, and irregularly infiltrated with polymorphonuclear leucocytes, mononuclear cells, and moderate numbers of eosinophiles. The adventitia was also edematous and infiltrated with similar cells. Only occasional fragments of the external elastic membrane remained. Healed lesions were present in the terminal branches of the coronary and renal arteries and were characterized by marked proliferation of the subendothelial connective tissues which in some vessels almost occluded their lumens. These vessels had intact, but altered, internal and external elastic tissue membranes. Their muscle coats were necrotic with marked separation of their fibers beneath the external elastic membrane. The adventitia was mildly infiltrated with lymphocytes and mononuclear cells and its fibers were moderately separated and discontinuous. The myocardium showed hypertrophy of its fibers, focal areas of round cell infiltration, and mild scarring with replacement of normal structures with fibrous connective tissue. The arteries within the myocardium showed no pathological changes. Arteries of the spleen and adrenal gland were similar to the terminal coronary and renal arteries. The parenchyma of the spleen and kidney confirmed the gross diagnosis of multiple anemic infarcts. The adrenal gland showed no changes aside from the vascular lesions in the periglandular connective tissue.

Case 2.—E. S., a 6½-year-old white female child, entered The Children's Memorial Hospital on Nov. 7, 1935, with convulsive movements. She was born at full term following a normal spontaneous delivery and weighed 7 pounds, 7 ounces. She was the fifth of eight siblings, three of whom succumbed in infancy and early childhood.

Her past medical history included pneumonia at 22 months, measles at 2 years, and pertussis at 5 years of age. In July, 1935, she developed scarlet fever from which she never made a complete recovery. In August, 1935, she was hospitalized elsewhere for two weeks because of facial and peripheral edema and signs of nephritis. She remained at bed rest at home for three weeks under daily medical observation.

For two days preceding her admission she complained of malaise, drowsiness, and headache. Several hours before admission she regurgitated her supper and shortly afterward exhibited continuous convulsive movements.

Physical examination on admission revealed a pale, malnourished child in constant motion. Her head was turned to the right, and her eyes, with dilated pupils, deviated in the same direction. There were continual jerking movements of the right arm and leg. The extremities were cold, and the skin surface was mottled with cyanosis. Râles could be heard throughout the chest. The heart apex was in the fifth left intercostal space, three-quarters of an inch beyond the nipple line. Its rhythm was regular at a rate of 160 to 180 per minute. Her temperature was 100° F., and her blood pressure was 170/128 mm. Hg. Her convulsions responded to rectal Avertin and intravenous magnesium sulfate and hypertonic glucose solutions.

The hemoglobin was 70 per cent, the red blood cells were 3.98 million, and the white blood cells were 33,900 per cubic millimeter. There were 84 per cent polymorphonuclear leucocytes, 15 per cent lymphocytes, and 1 per cent monocytes. Capillary fragility was normal. The urine was acid with a specific gravity of 1.015, a 2 plus albumin, and a 1 plus diacetic acid. Microscopically it showed many hyaline casts, occasional granular and waxy casts, many erythrocytes, and 20 to 30 white blood cells per high-

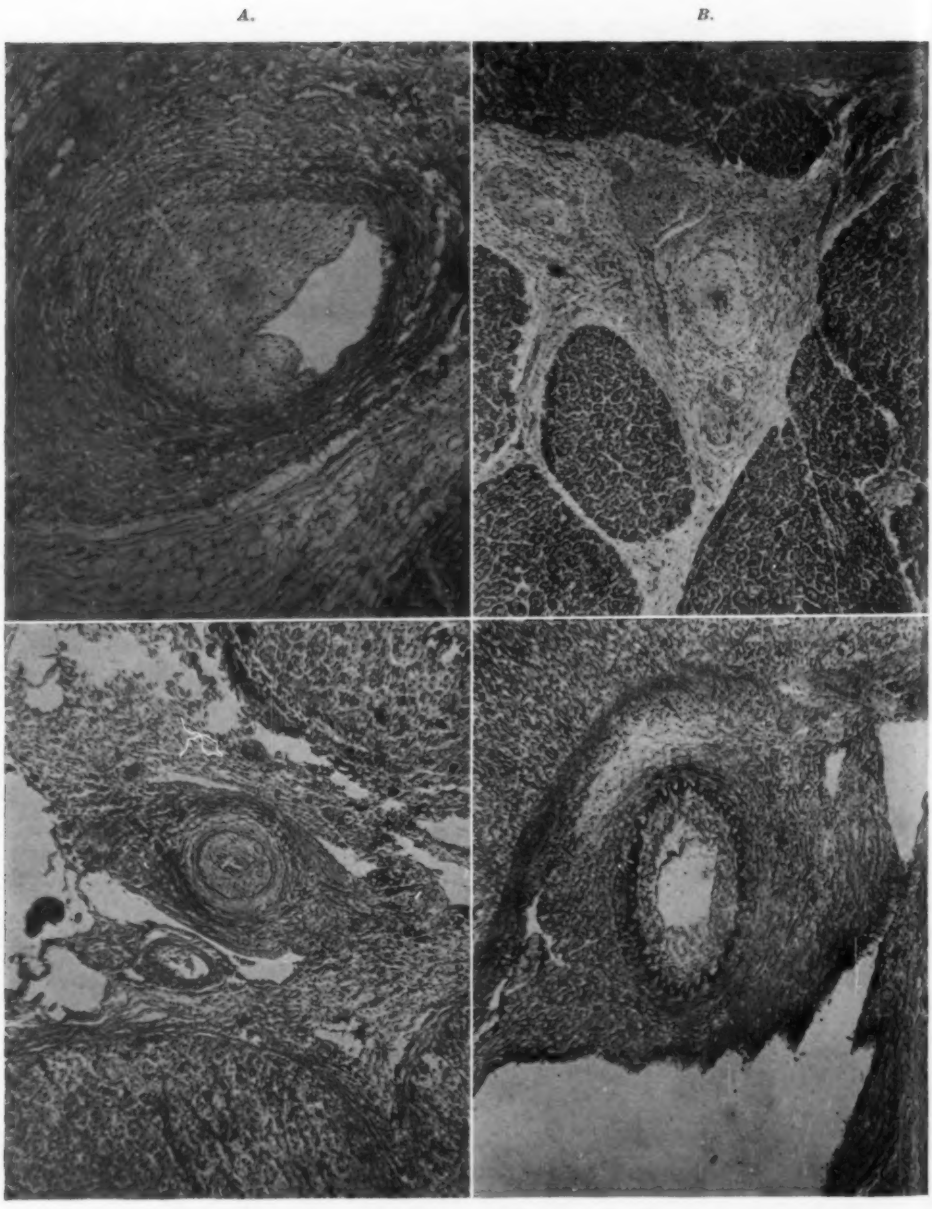

Fig. 6 (Case 2).—Typical arterial lesions found in polyarteritis nodosa. *A*, Coronary artery; *B*, pancreas; *C*, adrenal gland, and *D*, spleen.

power field. The blood Wassermann was negative. The nonprotein nitrogen was 45.4 mg. per cent, cholesterol was 150 mg. per cent, creatinine was 1.3 mg. per cent, uric acid was 7.3 mg. per cent, and the carbon dioxide content was 61 vol. per cent. The spinal fluid was clear but under pressure. The cell count and protein were normal. Repeated blood and spinal fluid cultures revealed no growth.

She improved and was able to take oral nourishment. A right hemiparesis developed and was thought to be due to a vascular accident. There was marked engorgement of the retinal veins, blurring of discs, and scattered hemorrhages, more severe in the left eye. One vein exhibited a localized dilatation. No definite papilledema was present.

Generally, the systolic pressure ranged above 150 mm. Hg and the diastolic between 110 and 130 mm. The temperature fluctuated between 101° and 105° F. A gallop rhythm and pericardial friction rub appeared. The liver edge descended to the level of the umbilicus. By the eighth hospital day no red blood cells were found in the urine, and by the twelfth day casts were absent.

On the twelfth hospital day she developed signs of a left otitis media, and a myringotomy was performed. Cyanosis and dyspnea increased, and she expired seventeen days following admission.

At necropsy the abdominal cavity contained about 50 c.c. of clear yellow fluid. The liver was enlarged 6 cm. below the right costal margin and was one and four-tenths times heavier than normal weight. The cut surface was pale and devoid of lobular markings. The spleen was of normal weight but exhibited a few fibrous adhesions to the contiguous peritoneal surface. The kidneys were slightly heavier than normal and were similar in appearance. The surfaces were uneven and marked by many large, irregular, depressed, stellate scars. These were purple in color and contrasted with the adjacent dark pink tissues. The capsules stripped with slightly increased resistance and were adherent to the pitted lesions. No gross infarcts were recognized. The major portions of the mucosa of the colon was diffusely hemorrhagic and its walls edematous. The right pleural cavity contained 80 c.c. of turbid yellow fluid. The parietal pleura on this side was injected. The lungs were dark in color and were increased in weight. On cut surface they were uniformly red and boggy but without evidence of pneumonic consolidation. The heart was one and four-tenths times heavier than normal and grossly revealed left myocardial hypertrophy.

Microscopic sections revealed only the healed stage of polyarteritis nodosa as described by Arkin.[48] Vascular lesions were found in the coronary arteries, kidney, spleen, adrenal gland, and pancreas. They were characterized by the presence of hyalinized fibrous scars poor in nuclei which in many instances almost or totally occluded the lumens. Subendothelial proliferation was marked in many vessels and was similar to the lesions observed in the terminal coronary and renal arteries in Case 1. In most vessels affected, the internal and external elastic fibers had entirely disappeared. Microscopic study further revealed hemorrhagic necrosis in the left lower lobe with focal fibrinous pleurisy, hemorrhagic pulmonary infarcts of the right upper lobe, hypostatic pulmonary congestion, myocardial hypertrophy, chronic focal glomerulonephritis, hemorrhagic colitis, and phlebitis of the right internal saphenous vein.

SUMMARY AND CONCLUSIONS

1. Polyarteritis nodosa, although found more commonly in recent years, is still an uncommon disease in childhood and especially so in infancy.

2. A total of fifty-two cases have been reported in the English literature in infancy and childhood up to

the age limit of 15 years. Of the fifty-two cases in infancy and childhood, eight cases occurred in infancy (under 2 years of age), seventeen between the ages of 2 and 8 years, and twenty-seven between the ages of 9 and 15 years.

3. Two cases of polyarteritis nodosa occurring in a boy, 4 months of age, and a girl, 6½ years of age, are reported.

The authors thank Grace Lawrence, Alice Nakoda, and Ilene Wilighman for their assistance and cooperation during the compilation of this article.

REFERENCES

1. Kussmaul, A., and Maier, R.: Deutsches Arch. f. klin. Med. **1**: 484, 1866.
2. Michaelis and Matani, quoted by Schreiber: Inaug. Diss., Königsberg, 1904.
3. Pelletan, P. J.: Clin. chir., Paris, 1810, vol. 1; quoted by Dickson: J. Path. & Bact. **12**: 31, 1908.
4. Rokitansky, K.: Denkschr. d. k. Akad. d. Wissensch., 1852, vol. 4; quoted by Dickson: J. Path. & Bact. **12**: 31, 1908.
5. Sawyer, C. F.: Necrotizing Arteritis (Periarteritis Nodosa), Surgery **6**: 717, 1939.
6. Schreiber, R.: Ueber Poliarteritis nodosa, Inaug. Diss., Königsberg, 1904.
7. Lamb, A. R.: Periarteritis Nodosa: A Clinical and Pathological Review of the Disease With a Report of Two Cases, Arch. Int. Med. **14**: 481, 1914.
8. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**: 870, 1923.
9. Gruber, G. B.: Virchows Arch. f. path. Anat. **245**: 123, 1923; **258**: 441, 1925.
10. Rothstein, J. L., and Welt, S.: Periarteritis Nodosa in Infancy and in Childhood, Am. J. Dis. Child. **45**: 1277, 1933.
11. Dickson: J. Path. & Bact. **12**: 31, 1908.
12. Wordley, E.: Lancet **2**: 927, 1923.
13. Gray, J.: J. Path. & Bact. **29**: 245, 1926.
14. Barnard, W. G., and Burbury, W. M.: Gangrene of the Fingers and Toes in a Case of Polyarteritis Nodosa, J. Path. & Bact. **39**: 285, 1934.
15. Neale, A. V., and Whitfield, A. G. W.: Rheumatism and Its Relation to Periarteritis Nodosa, Brit. M. J. **2**: 104, 1934.
16. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa (Necrotizing Arteritis) Associated With Rheumatic Heart Disease, With Note on Abdominal Rheumatism, Arch. Int. Med. **54**: 170, 1934.
17. Krahulik, L., Rosenthal, M., and Loughlin, E. H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood With Meningeal Involvement: Report of Case With Study of Pathologic Findings, Am. J. M. Sc. **190**: 308, 1935.
18. Dunbar, J. C.: Periarteritis Nodosa With Associated Thrombocytopenic Purpura, Bull. School Med. Univ. Maryland **20**: 138, 1936.
19. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**: 993, 1936.
20. Vining, C. W.: A Case of Subcutaneous Lesions With Recovery, Arch. Dis. Childhood **13**: 31, 1938.
21. Hoyne, A. L., and Steiner, M. M.: Periarteritis Nodosa Complicating Scarlet Fever (With Unusual Syndrome of Nephritis and Polyneuritis), Am. J. Dis. Child. **59**: 1271, 1940.
22. Grant, R. T.: Observations on Periarteritis Nodosa, Clin. Sc. **4**: 245, 1940.
23. Keeth, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, J. PEDIAT. **18**: 494, 1941.
24. Maxwell, C. S., and Maxson, W. T.: Cerebral Type of Periarteritis Nodosa; Case Report, Internat. Clin. **2**: 217, 1941.
25. Coe, M., Reisman, H. A., and De Hoff, J.: Periarteritis Nodosa in a Nine-Year-Old Child, J. PEDIAT. **18**: 793, 1941.
26. Stewart, A. M.: Periarteritis Nodosa, Proc. Roy. Soc. Med. **35**: 18, 1941.
27. Goldman, B. A., Dickens, K. L., and Schenken, J. R.: The Apparent Cure of Periarteritis Nodosa With Sulfapyridine, Am. J. M. Sc. **204**: 443, 1942.
28. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, Bull Johns Hopkins Hosp. **71**: 123, 1942.
29. Jones, G. M., Jr.: Periarteritis Nodosa, Ann. Int. Med. **16**: 920, 1942.
30. Malamud, N.: A Case of Periarteritis Nodosa With Decerebrate Rigidity and Extensive Encephalomalacia in Five-Year-Old Child, Univ. Hosp. Bull., Ann Arbor **10**: 43, 1944.
31. Scott, E. P., and Potondo, C. C.: Periarteritis Nodosa, J. Pediat. **25**: 306, 1944.
32. Wilmer, H. A.: Two Cases of Periarteritis Nodosa Occurring in the First Month of Life, Bull. Johns Hopkins Hosp. **77**: 275, 1945.
33. Logue, R. B., and Mullins, F.: Polyarteritis Nodosa: Report of Eleven Cases With Review of Recent Literature, Ann. Int. Med. **24**: 11, 1946.
34. Diaz-Rivera, R. S., and Miller, A. J.: Periarteritis Nodosa: A Clinicopathologic Analysis of 7 Cases, Ann. Int. Med. **24**: 420, 1946.

35. Day, H. W., and Hesser, H. H.: Periarteritis Nodosum and Wilm's Tumors—Case Report, J. Kansas M. Soc. **47**: 202, 1946.
36. Peale, A. R., Gildersleeve, N., and Lucchesi, P. F.: Periarteritis Nodosa Complicating Scarlet Fever, Am. J. Dis. Child. **72**: 310, 1946.
37. Miller, H. G., and Daley, R.: Clinical Aspects of Polyarteritis Nodosa, Quart. J. Med. **15**: 255, 1946.
38. Pickard, C. M., Owen, J. G., and Dammin, G. J.: Aneurysms of the Coronary Arteries Due to Polyarteritis Nodosa Occurring in an Infant: Report of a Case With Coronary Artery Thrombosis and Myocardial Infarction, J. Lab. & Clin. Med. **32**: 1513, 1947.
39. Bradley, E. J.: Periarteritis Nodosa in Childhood, J. PEDIAT. **31**: 78, 1947.
40. Fisher, R. S., and Howard, H. H.: Unusual Roentgenograms in a Case of Periarteritis Nodosa, J. Urol. **60**: 398, 1948.
41. Neale, A. V.: Polyarteritis in Childhood, Arch. Dis. Child. **24**: 224, 1949.
42. Sinclar, W., Jr., and Nitsch, E.: Polyarteritis Nodosa of the Coronary Arteries, Am. Heart J. **38**: 898, 1949.
43. Klein, S. P.: Periarteritis Nodosa, Arch. Int. Med. **84**: 983, 1949.
44. Taylor, A. W., and Jacoby, N. W.: Acute Polyarteritis Nodosa in Childhood, Lancet **2**: 792, 1949.
45. Prouty, M., and Schafer, E. L.: Periarteritis Nodosa Associated With Ratbite Fever Due to Streptobacillus Moniliformis (Erythema Arthriticum Epidermicum), J. PEDIAT. **36**: 605, 1950.
46. Gemson, B.: Periarteritis Nodosa in an 11-Year-Old Boy, J. PEDIAT. **36**: 813, 1950.
47. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.
48. Arkin, A.: Clinical and Pathologic Study of Periarteritis Nodosa; Report of Five Cases, One Histologically Healed, Am. J. Path. **6**: 401, 1930.
49. Carey, R. A., Harvey, A. McG, and Howard, J. F.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on the Course of Disseminated Lupus Erythematous and Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **87**: 425, 1950.

ATOPIC DERMATITIS IN INFANTS AND CHILDREN

ALBERT ROWE, JR., M.D., AND ALBERT H. ROWE, M.D.
OAKLAND, CALIF.

ATOPIC dermatitis has been studied in 100 consecutively encountered infants and children treated in private practice within the last three years. There were fifty-one males and forty-nine females. Onset occurred within the first two years of life in 90 per cent, and bore no relationship to seasons, except in proved pollen sensitive patients when the dermatitis was exaggerated or only present during the spring, summer, or early fall. The disease was perennial in 67 per cent with definite exacerbations during the spring and summer in 28 per cent. The majority of patients exhibited other allergic manifestations. Allergic rhinitis was present in 44 per cent, bronchial asthma in 26 per cent, and probable gastrointestinal allergy was present in 11 per cent. A family history of allergy was obtained in 65 per cent of cases, eczema, asthma, and allergic rhinitis being most frequent. Symptomatic therapy had been received by 68 per cent of patients, and 61 per cent had been subjected to ineffectual diet manipulation prior to being seen. It is to be noted that in only one case inhalant desensitization therapy previously had been instituted.

CAUSES OF ATOPIC DERMATITIS

As in the study of all manifestations of atopic allergy, food, inhalant, drug, and infectant allergies were considered as possible causes of atopic dermatitis. As reported previously by one of us (A. H. R.)[1] and recently by Tuft[2] food and inhalant allergies are the important causes of atopic dermatitis. Hill[5] for many years, along with Stoesser[6] and Glaser,[7] has recorded the frequency of food allergy. Occasional drug allergy and infectant allergy were encountered in this series. Though contact allergy needs constant consideration as stated by Hill, we have been unable to confirm the importance ascribed to it by Cooke.

METHODS OF STUDY AND TREATMENT

A detailed history was obtained to reveal probable food, inhalant, or drug allergy. Physical examination, complete blood count, and urinalysis were done routinely. Scratch or puncture testing with important ingestant and inhalant allergens were performed on all patients. Intradermal testing, as described below, was reserved for those patients suspected of being inhalant sensitive, especially when environmental control alone was ineffective. Such intradermal testing was done by our modification of the serial dilution titration technique of Rinkel,[3] and frequently proved a valuable guide to desensitization therapy. We have observed severe exacerbations of dermatitis from scratch testing, and in former years from intradermal testing, even with 1 to 5 billion dilutions. The fallibility of the skin test in food allergy, and in inhalant allergy, especially when the latter causes atopic dermatitis, will be discussed later. Elimination diets were used in 95 per cent of cases for study of possible food

This work was supported in part by the Armour-Gerber Fund.

allergy. Environmental control was instituted in 55 per cent, inhalant desensitization was given in 58 per cent, and vaccine therapy for secondary infection was administered in 10 per cent. Our recently devised filter tent was utilized to study and treat inhalant allergy in 12 per cent of cases. Nonspecific therapy included use of ointments, local compresses, parenteral antibiotics, restraints, and hospitalization.

FOOD ALLERGY

Food allergy was the sole cause of atopic dermatitis in 44 per cent. It also was associated with inhalant allergy in 41 per cent. Food allergy should be suspected when the onset of dermatitis is in the first few months of life, if the dermatitis is perennial in nature, and when exacerbations occur in the fall and winter months, with relative or complete relief during the spring or summer. A carefully obtained dietary history at times reveals offending foods. Occasionally allergenic foods are indicated by definite skin reactions by the scratch or puncture test. The frequency of false positive and false negative reactions however is generally realized.

In most cases therefore chronic food allergy must be studied and controlled by the use of trial diets, over a two- to four-week or longer period. Such prolonged diet trial is necessary because previously eaten foods remain in the body, as do drugs, for more than a few days, and because of the time required for cells of affected tissues to return to normal structure and function.

Our standardized elimination diets[4] which furnish a list of allowed foods, detailed menus, and recipes for bakery products, and insure adequate nutrition, were used for this study of food allergy in 95 per cent of cases. Soy bean milk, or our strained meat formula utilizing Gerber's or Swift's strained meat, water, potato starch or arrowroot, sugar, salt, calcium, and sesame oil may be safely and completely substituted for cow's milk. This meat formula is indicated when allergy or intolerance to soy and other legumes is present.

Strained Meat Formula (Rowe)

Strained lamb 15.6% P 4.5% F	1 cup 8 oz.
or	
Strained beef 17.7% P 3% F	¾ cup 6 oz.
Sesame oil or soy oil	3⅓ Tbsp.
Sugar	2 Tbsp.
Potato starch flour 83% C	
or	2½ Tbsp.
Tapioca flour 88% C	
Calcium carbonate	1 tsp.
Salt	½ tsp.

Water to make a volume of 1,000 c.c. or 4½ cups.

Cook the starch, salt, and sugar in one cup of water for ten minutes. Then add meat, oil, and sufficient water to make a volume of 4½ cups, and cook with low heat for ten to fifteen minutes. Reduce starch for thinner product.

After relief is assured individual foods are added every four to seven days with subsequent elimination of any which reproduce or exaggerate eczema. Milk, cereal grains, egg, citrus fruits, fish, spices, and condiments were found to be the most common offenders.

Diet manipulation had been carried out previously in 61 per cent of patients. In many instances lack of relief could be attributed to incomplete elimination of allergenic foods, the exclusion of only one or two instead of all the offending foods, or the use of diet trial for too brief a period. We have found that marked food

allergy requires the elimination of all traces of allergenic foods, and their products, and that foods denatured by heat frequently produce allergic symptoms. Medications and vitamin preparations containing traces of allergenic foods, such as fish oils and cereals, occasionally were responsible for the dermatitis. Synthetic vitamins therefore were advised. Occasional allergy to vitamins per se must be remembered.

Pollen allergy[1] should be suspected when the onset or increase of eruption occurs in the spring, summer, or early fall, with complete or partial relief during the winter. Occasionally atopic dermatitis continuing in the winter months has been due to pollens retained in dust in rugs, furniture, and heating systems. Such pollen allergy was more frequently indicated by skin tests by the scratch, puncture, and intradermal

Fig. 1.—Our filter tent* for establishing dust and pollen free environment in hospital wards. Parts include plastic hood, with zippers at corners; oil-impregnated steel wool removable filter; damper at apex of intake cone; electrically driven squirrel cage intake fan.

INHALANT ALLERGY

Inhalant allergy alone was responsible for atopic dermatitis in 15 per cent of cases, and in association with food allergy in 41 per cent. The frequency of inhalant sensitivity as the cause increases after the first year.

*Unit available from Aladdin Heating Corp., 2222 San Pablo Ave., Oakland, Calif.

methods than was food allergy. However, in approximately 15 to 20 per cent of proved pollen sensitive children positive reactions were not obtained. We strongly advise against initial intradermal testing with strong antigens because of possible exaggeration of dermatitis. Inhalant allergy, moreover, is indicated by relief of derma-

titis arising in a pollen- and dust-free environment in the home or hospital. Commercial or homemade window filters, utilizing impregnated paper filters, may be installed in the window to rid all incoming air of dusts and pollens. Our recently devised filter tent (Fig. 1) for a crib in a hospital ward obviates the necessity of an expensive air-conditioned room.

Our therapy has utilized multiple antigens containing all important pollens present in the area of residence, emphasizing those to which definite scratch or puncture reactions have been obtained. Initial doses frequently must be extremely small, often in the million or billion dilutions. Before treatment is begun intradermal testing with serial dilutions is done by Rinkel's[3] method to determine the initial dose. We have modified Rinkel's method as follows:

The lowest dilution necessary to produce a 7 mm. wheal and 20 mm. surrounding zone of erythema is determined and a dilution 100 times weaker is given as the first desensitizing injection. Using dilutions in multiples of 10, the weakest initial dilution for titrations may be in the millions or billions according to the degree of suspected allergy. Initial doses of 1:5,000 billion or weaker for infants or young children have been necessary at times to prevent exaggeration of dermatitis, and repetition of such doses every three to five days for weeks, especially during the pollen season, has gradually reduced the dermatitis. Doses are gradually increased at regular intervals thereafter, providing no increase in the dermatitis is produced by injections. At times an increase above a helpful desensitizing dose has been impossible for weeks or even months. If exacerbations result from therapy the amount of administered antigen is reduced or serial titrations repeated. When intradermal testing with serial dilutions fails to reveal a helpful desensitizing dose clinical titration alone must be used as follows: Initially an extremely weak dilution is administered hypodermically. Subsequent injections are gradually increased until slight exacerbation of dermatitis occurs. Doses are then reduced below this reacting level and slowly increased as tolerated thereafter.

During pollen seasons it is necessary frequently to reduce drastically the dose. An exacerbation of dermatitis by desensitization therapy, although disturbing to the patient, is of definite diagnostic value. The most satisfactory results have been obtained with perennial desensitization for a twelve- to twenty-four-month or longer period.

HOUSE DUST ALLERGY

House dust allergy should be suspected when atopic dermatitis is perennial or flare-ups occur during the late fall, winter, or early spring months when houses are closed and furnaces frequently are in use. The afore-mentioned exaggeration of food allergy in the fall and winter months must also be remembered. House dust allergy is usually indicated by positive scratch or puncture tests although positive reactions are not always associated with clinical symptoms. Intradermal titrations are done with that care and technique advised in pollen sensitive patients. Strict environmental control in the bedroom and frequently

throughout the entire house usually is necessary for the diagnosis and control of house dust sensitivity. Our filter tent may be of value in hospital or home. Elimination of dusts from heating systems is most important. Desensitization is carried out as described for pollen allergy.

ANIMAL EMANATIONS, MISCELLANEOUS INHALANTS AND FUNGI

Animal emanations, miscellaneous inhalants and fungi always were suspected but proved of minor importance to dust and pollen. A few patients gave large scratch reactions to animal emanations, cottonseed, flaxseed, orris root, and pyrethrum. Moreover clinical evidence of sensitivity to one or more of these inhalants was found occasionally in the absence of definite scratch or puncture reactions. Environmental control and at times desensitization with those allergens which could not be eliminated from the environment was necessary.

TABLE I. ATOPIC DERMATITIS IN INFANTS AND CHILDREN (100 CASES)

Sex		*Distribution*	
Males	51	Face and neck	67
Females	49	Flexural	57
Age at Onset		Upper extremities	61
Birth to 3 months	35	Lower extremities	59
3 months to 1 year	35	Torso	40
1 to 2 years	21	*Scratch Tests*	
2 to 8 years	8	Foods	68
8 to 16 years	1	Pollens	59
Previous Duration of Dermatitis		Trees 9	
Birth to 1 month	3	Spring 30	
1 to 6 months	17	Fall 20	
6 to 12 months	14	House dust	29
1 to 2 years	31	Miscellaneous inhalants	21
Over 2 years	35	Animal emanations	22
Seasonal Onset and Exacerbation		Fungi	4
Onset		*Specific Treatment*	
Fall and winter	52	Elimination diets	95
Spring and summer	43	Environmental control	55
Exacerbations		Filter tent	12
Fall and winter	23	Desensitization	58
Spring and summer	28	Pollens 55	
Perennial	67	House dust 28	
Other Manifestations of Allergy		Animal emanations 8	
Urticaria	1	Fungi 1	
Nasal	44	Vaccine	10
Bronchial	26	*Nonspecific Treatment*	
Gastrointestinal	11	Ointments	67
Positive Environmental History		Antihistaminics 4	
House dust	15	Antibiotics 21	
Animals	12	Coal tar 13	
Contactants	2	others 29	
Positive Family History of Allergy		Compresses (Burow's or saline)	12
Eczema	37	Sulfadiazine, oral	1
Asthma	42	Penicillin, parenteral	3
Nasal	36	Restraints	14
Gastrointestinal	1	Hospitalization	11
Previous Therapy		*Causes of Atopic Dermatitis*	
Symptomatic	68	Foods alone	44
Environmental control	3	Inhalants alone	15
Desensitization	1	Foods plus inhalants	41
Diet manipulation	61	*Results*	
None	6	Excellent	66
		Good	18
		Poor	4
		Fair	12

RELIEF OF SYMPTOMS

The relief of dryness, scaling, cracking, and erythema was obtained with ointments containing Lassar's paste, ammoniated mercury, coal tar, and antihistaminics. Compressing with salt solution or 1:50 Burow's solution was instituted when oozing was prominent. Oral antihistaminics occasionally relieved itching. We encountered two extremely severe generalized dematoses due to allergy to antihistaminics. Saline or plain water baths one to three times a day have been given. Application of mineral oil, petrolatum, or 4 per cent glycerin solution thereafter has softened the skin.

Local application of 1:2,000 epinephrine solution rubbed into affected areas relieved pruritus in certain patients. For secondary infection ointments containing bacitracin, tyrothricin, or Vioform, and penicillin, aureomycin, or chloramphenicol were locally used, or given orally or parenterally, and were of definite benefit. Local tissue allergy developed more frequently with the use of penicillin and tyrothricin than with bacitracin ointment. When scratching impaired recovery, restraining was instituted with carefully placed wrist and arm ties, with or without elastic bandages and arm splints.

Complications included anemia, pyoderma, bronchial asthma, and allergic rhinitis as shown in Table I. In this series the most serious complication was Kaposi's varicelliform dermatitis which disabled a 9-month-old girl for over one month.

RESULTS

With the employed methods of study and treatment of specific causes and symptoms, good or excellent results were obtained in 84 per cent of cases. These good results emphasize the importance of thorough and experienced study and treatment of inhalant along with food allergy. Desensitization with inhalants which could not be excluded from the patient's environment usually was necessary. Dilutions of antigen must never exaggerate the dermatitis, and often, especially in young children, must be given in the weak billion dilutions. When food allergy alone is responsible good or excellent results were frequently obtained in two to four months.

Follow-up study has revealed that elimination of offending foods is necessary for periods varying from six months to as long as five years in many patients, and frequently establishes tolerance in from six months to five or more years. When inhalant allergy is the sole or a contributing cause, desensitization therapy is often necessary for one to three years. In some cases the degree of relief at the end of the first year was only 50 to 75 per cent, and increased significantly during the second year of our control.

SUMMARY

1. A study of atopic dermatitis in private practice in 100 consecutively encountered infants and children over a three-year period reveals equal distribution between sexes with onset in the first two years of life in 90 per cent. The dermatitis was exaggerated in the pollen seasons when due to pollen, and often in the fall to spring when due to foods, and at times to house dust and environmental allergens. Dermatitis was perennial in 67 per cent with exacerbation during the spring and summer in 28 per cent.

2. The majority of patients exhibited other allergic manifestations, and a family history of allergy was obtained in 65 per cent of cases.

3. Food, inhalant, drug, and infectant allergies were considered possible causes. Food and inhalant allergies proved to be most important. A detailed history, physical examination, and cautious skin testing by both scratch and intradermal methods were the most effective diagnostic procedures. Scratch or puncture testing with important ingestants and inhalants was performed on all patients, and intradermal testing reserved for those suspected of being inhalant sensitive, especially when environmental control alone was not effective. Intradermal testing was performed by our modification of the serial titration technique of Rinkel.

4. Elimination diets were used in 95 per cent of cases for study of suspected food allergy. Environmental control was instituted in 55 per cent, inhalant desensitization given in 58 per cent, and vaccine therapy for secondary infection in 10 per cent. Our recently devised filter tent was used for the study and treatment of inhalant allergy in 12 per cent.

5. Food allergy was the sole cause of atopic dermatitis in 44 per cent, and was associated with inhalant allergy in 41 per cent. Inhalant allergy alone was responsible in 15 per cent, and in association with food allergy in 41 per cent. The frequency of inhalant sensitivity increases after the first year.

6. The utilization of extremely weak dilutions of inhalant antigens is stressed. In the majority of inhalant sensitive individuals an appropriate initial desensitizing dose could be approximated by the serial dilution titration technique. However clinical titration alone was occasionally necessary.

7. The control of symptoms especially pruritus is discussed.

8. With study and treatment of specific causes, good or excellent results were obtained in 84 per cent of cases. These good results emphasize the importance of thorough and experienced study and treatment of inhalant allergy along with food allergy. In some cases the degree of relief at the end of the first year was only 50 to 75 per cent, and increased significantly during the second year of control.

REFERENCES

1. Rowe, Albert H.: Clinical Allergy, Philadelphia, 1937, Lea & Febiger.
—: Dermatitis of the Hands Due to Atopic Allergy to Pollen, Arch. Dermat. & Syph. 53: 437, 1946.
—: Atopic Dermatitis of the Hands Due to Food Allergy, Arch. Dermat. & Syph. 54: 683, 1946.
2. Tuft, Louis: Atopic Dermatitis—Etiology and Clinical Management, California Med. 73: Sept., 1950.
3. Rinkel, Herbert: Inhalant Allergy—Coseasonal Application of Serial Dilution Testing (Titration), Ann. Allergy, Sept.-Oct., 1949.
4. Rowe, Albert H.: Elimination Diets and the Patient's Allergies, ed. 2, Philadelphia, 1944, Lea & Febiger.
—: Elimination Diets for the Study and Control of Food Allergy, Quart. Rev. Allergy & Applied Immunol. 4: 227, 1950.
5. Hill, L. W.: Eczema in Infancy and Childhood, New England J. Med. 242: 286, 1950.
6. Stoesser, A. V.: Clinical Evaluation of Soy Bean Food in Eczema of Child, Ann. Allergy 2: 404, 1944.
7. Glaser, J.: Treatment of Eczema (Atopic Dermatitis) in Infancy. J. A. M. A. 137: 527, 1948.

Case Reports

FULMINATING MUMPS MENINGOENCEPHALITIS WITH RECOVERY

SIMON B. MENDELSBERG, M.D.
BROOKLYN, N. Y.

THE report of a single case of mumps meningoencephalitis, even of extreme severity, would scarcely be justified were it not for the unusual clinical and laboratory findings which were encountered. Briefly, these consisted of hyperpyrexia, extensive periparotid edema, and prolonged coma following convulsions. In association, there were a relatively unaltered spinal fluid, quadriplegia with cranial nerve involvement, and a profuse salivation.

CASE REPORT

J. W., a 28-month-old white, Jewish male, was admitted to the Maimonides Hospital, Israel Zion Division, Brooklyn, N. Y., on Oct. 2, 1950, at 8:30 A.M. because of a generalized convulsion and a temperature of 107.2° F.

The present illness began two nights previously with a temperature of 102° F. On Oct. 1, the day prior to admission, another physician had injected penicillin and prescribed aureomycin by mouth. About one hour before admission, the child suddenly developed a generalized seizure. Upon examination, some twenty minutes later, the patient was lying quietly between ice cold sheets, completely alert and oriented. Except for a mildly congested nasopharynx there were no significant findings, but because of the temperature of 107.2° F., he was given 600,000 U. of aqueous procaine penicillin intramuscularly and promptly hospitalized.

The family history was noncontributory.

The past history is of some clinical interest. The child was delivered normally following an uneventful pregnancy. At birth he presented a marked asymmetry of the head, face, and jaw. An x-ray was taken to rule out cortical hyperostosis. There were, in addition, an oblique position of the tongue, being higher on the right side, and a right torticollis, which have persisted. For almost the entire first year of life there was a congenital stridor of such severity as to contraindicate anything more than conservative treatment of the wryneck. This child's growth and nutrition were maintained at satisfactory levels in spite of very frequent upper respiratory infections which were treated with sulfonamides and/or the antibiotics.

On admission, the child appeared fairly comfortable despite the high temperature. The blood count showed a hemoglobin 12.4 Gm., red blood cells 5,000,000, white blood cells 15,550, and a moderate shift to the left. The spinal fluid was under normal pressure with no cells, normal sugar, protein, and chloride content. Cultures of the blood, spinal fluid, and nasopharynx were negative. The urine was normal as were the blood chemistries (urea, total protein, calcium, phosphatase, chlorides, carbon dioxide, sodium, and potassium). Serology and agglutination studies for typhoid, etc., also were negative. 600,000 U. of procaine penicillin intramuscularly, b.i.d., and 100 mg. of aureomycin per os, q.i.d., were ordered. Later in the day, bilateral facial swelling was noted by the house staff. Examination at 5 P.M. revealed marked swelling of both parotids, but it was felt that the child was now too ill to warrant transfer to a contagious disease hospital. Three hours later, following several tonic spasms, the patient lapsed into deep coma which persisted for almost a week. The striking finding at this time, however, was a bilateral edema

which had spread far beyond the confines of the parotids to involve the entire face and head above and extending well below the mandible onto the neck. On palpation into the edema, one could outline the parotids by differential resistance. Rapid respirations accompanied by retraction above and below the sternum and by profuse salivation made a Trendelenburg position mandatory. The child appeared to be in extremis. Continuous intravenous fluids and oxygen were begun. Other therapy consisted of aqueous penicillin 500,000 U. intramuscularly, q. 3. h., 100 mg. aureomycin intravenously, q.i.d., injections of aqueous cortical extract q. 4. h., and parenteral vitamins.

The following morning the temperature was 104° F. with no essential change in the general condition. The coma and edema were still marked. Rhonchi were heard throughout the chest and constant suction was required to remove the excessive salivation. Right internal strabismus due to involvement of the right sixth cranial nerve became evident. A second spinal tap was performed which again was normal except for an increased protein. Blood samples for viral studies were drawn at this time and again one week later, but were lost due to a laboratory accident. A portable chest x-ray was normal. During the next few days the temperature dropped by lysis and the edema gradually subsided, first on the right side and then on the left.

The first function to return was deglutition, and by Oct. 7 the youngster could be aroused sufficiently to take an occasional sip. He next began to respond with searching eye movements to his mother's voice or childhood records, but for the most part he whined incessantly and was not in contact. The mucus was still profuse. A widespread aphthoid stomatitis had developed probably due to the almost constant suction. On Oct. 10, the intravenous therapy was discontinued. At this time he was taking liberal amounts of fluids and some strained solids. With cessation of the intravenous therapy, during which time the child had been in the customary restraints, it was first observed that there was a complete quadriplegia. The deep tendon reflexes were diminished to absent. That day his temperature rose to 103.4° F., and the white blood count to 18,000 but this was interpreted as being due to a thrombophlebitis caused by the aureomycin which had been administered in each of the extremities. The child was seen in consultation at this time by Dr. Murray Bass who felt that the patient had a mumps meningoencephalitis despite the leucocytosis and normal spinal fluid. He pointed out that an extensive edema with mumps is not unknown and has been described both by Abt and Gellis. He suggested that small doses of atropine be given to control the salivation. On administration of 1/1000 gr. atropine sulfate by hypodermic, the child turned brick red and the drug was discontinued.

On Oct. 11, a third lumbar puncture was performed and revealed 40 white cells, 90 per cent of which were lymphocytes. The other constituents were normal. The fever gradually subsided by Oct. 13, and thereafter remained normal. On Oct. 11, slight motions became apparent in the feet and on each succeeding day became more manifest as though a reverse Landry's were occurring. When he began to move his hands, the motions initially were clumsy and athetoid. After several more days, he could hold up his head in a wobbly fashion and would turn, using searching ocular movements in response to being called. Crude attempts at phonation were next evident. Right abducens involvement cleared considerably by Oct. 21, so that the right eye could be made to move beyond the midline. The patient was able by this time to sit unassisted and carried out all commands appropriate for his age level. On Oct. 16 and 23, blood samples were drawn for viral studies and were both reported

as being positive against mumps in dilutions of 1:256. Banthine in doses of 10 mg., t.i.d., was begun on Oct. 22 in the hope that its anticholinergic action might control the salivation which had continued to be very annoying. There was some response but it was not dramatic. The youngster was discharged on Oct. 26, after twenty-four days of hospitalization, in apparently good condition. When seen at the office one week later, he appeared to have recovered completely from his illness except for a mild extraocular muscle imbalance and some thickness of speech.

COMMENT

It is well documented that central nervous system involvement in mumps may precede, be concomitant with, follow, or occur independently of parotitis. It would perhaps be more accurate to say "manifest parotitis," and Lightwood[1] is probably justified in stating that the term "epidemic parotitis" is unduly restrictive in its implications. Spinal pleocytosis is found frequently even without clinical neurologic signs. In the case here reported the blood showed a leucocytosis where a normal or leucopenic response is usual. When the parotids did swell, the swelling was dramatic in onset and in three hours was accompanied by the extensive edema. This edema was pittable in contrast to the gelatinous type which Heller[2] reported as being so characteristic. The severity of the convulsions and the depth of the coma were unusual for a case of mumps. Especially noteworthy were the absence of pleocytosis and the lack of increased spinal protein, although these conditions may rarely obtain. Kilham,[3] in a carefully studied series of twenty-five cases of mumps meningoencephalitis, found a pleocytosis in every instance. No count fell below 100 cells per cubic centimeter in the first week, and one peak of 2,920 cells was reached. In our case no cells were obtained on the third and fourth days of the disease and only 40 cells on the eleventh day. The quadriplegia and cranial nerve involvement displayed by this child are quite uncommon. Serum amylase, antiagglutination determinations, and viral cultures were not done.

The technique of complement fixation has become a distinct aid both in the diagnosis and the differential diagnosis of mumps and other viral diseases. In mumps the titer rises rapidly almost from the onset of the disease and attains a plateau in about two weeks. The antibody level usually begins to fall off after six weeks to two months, although it may occasionally persist at elevated levels for several months longer. Because of the laboratory accident referred to, titers in the sera of the fourth and eleventh days of the illness were not available so that a rise in titer was not demonstrable. However the sera of the seventeenth and twenty-fourth days of the disease revealed a concentration of 1:256 which may be considered diagnostically significant. Although a single high titer during the convalescent phase may be misleading, it is pertinent that Enders[4] makes the statement that "such high titers may be regarded as presumptive evidence since it has been shown by many hundreds of tests in normal individuals that the titer is rarely 1:96 and has only once been found to exceed 1:192." The titer takes on additional weight when one considers that the patient is a single offspring who is only 2 years old. The probable source of contagion was a short-lived attendance at a local nursery school two to three weeks prior to his illness.

REFERENCES

1. Lightwood, R.: Myelitis From Mumps, Brit. M. J. 1: 484, 1946.
2. Heller, G.: Gelatinous Edema: Pathognomonic Sign in Mumps, Am. J. Dis. Child. 78: 903, 1949.
3. Kilham, L.: Mumps Meningoencephalitis With and Without Parotitis, Am. J. Dis. Child. 78: 324, 1949.
4. Enders, J. F.: Techniques of Laboratory Diagnosis, Tests for Susceptibility, and Experiments on Specific Prophylaxis, J. PEDIAT. 29: 129, 1946.

SICKLE-CELL ANEMIA

Report of a Case in a Newborn Infant

Frederick J. Heldrich, Jr., M.D.
Baltimore, Md.

SICKLE-CELL anemia has rarely been diagnosed in infancy, and in childhood increases in direct proportion to increasing age.[1] The purpose of this paper is to present a proved case of sickle-cell anemia occurring in a newborn Negro infant.

CASE REPORT

History.—The patient, a newborn Negro female was delivered spontaneously, under aseptic conditions on Jan. 15, 1951, after an uncomplicated labor. Routine aspiration was accomplished. No abnormalities were noted. Birth weight was 2,693 grams. The infant was immediately removed to the newborn nursery.

The mother was an obese, 36-year-old Negro, para 2011. Blood type O, Rh positive, serologic test for syphilis negative. She had been followed in the prenatal clinic and was known to have sicklemia. Hemograms during her pregnancy at no time revealed evidence of a hemolytic anemia. The prenatal course was complicated by hyperemesis in the first trimester. Her past history revealed a spontaneous abortion at eight weeks' gestation in 1945. She has a 10-year-old daughter, who, at the present time, is being followed in the Pediatric Outpatient Department of University Hospital because of sickle-cell anemia which was first discovered when she was 1½ years of age. The paternity is identical for this patient and the one being presented. The father is a 42-year-old Negro, blood group B, Rh positive, serologic test for syphilis negative, with a hemoglobin of 110 per cent, 16.1 Gm., and sicklemia of 10 per cent. He has never been treated for anemia and has enjoyed excellent health.

Physical Examination.—Routine physical examination was done on the first day of life and revealed a Negro female weighing 2,665 grams. The cry was lusty. Circumference of the head was 32.5 cm., chest 28.5 cm., and length 49 cm. Movements were active. There was no bulging of the fontanels or overlapping of the suture lines. Moro reflex was elicited. An icteric tinge of the sclera was noted. No generalized adenopathy. Lungs were clear. A harsh systolic murmur was present, heard best substernally and just to the left of the sternum in the fifth interspace. No cord bleeding was noted. The liver and spleen were not palpable. Anus was patent.

Course in the Hospital.—The infant was put on the routine newborn feedings, consisting of nothing by mouth for the first twelve hours, then 1½ ounces of glucose every four hours for the next twenty-four hours. After the first thirty-six hours she was put to breast. She was given the routine prophylaxis for gonorrheal ophthalmia, 20,000 units of penicillin intramuscularly. A hemogram was done on the mother the day after delivery and revealed a hemoglobin of 83 per cent, 12.1 Gm., hematocrit 34 mm., 3.91 million erythrocytes, and sickling of 90 per cent of the erythrocytes by the sodium bisulfite method. These values were the same on the second post-partum day. After the first twenty-four hours of life the infant was kept in the room with the mother. On the third day of life the mother reported "a few drops of red blood" came from the nares following a sneeze. There were no other complaints. Examination of the infant at this time revealed no

From the Department of Pediatrics, University Hospital and University of Maryland School of Medicine.

change from the initial physical except for more marked scleral icterus. A hemogram was done on the fourth day of life and revealed a hemoglobin of 92 per cent, 13.3 Gm., 4.27 million erythrocytes, and 30 per cent sickling by the sodium bisulfite method. The infant was observed daily and the scleral icterus was noted to increase, reaching a peak on the eighth day of life and then gradually subsiding until it was no longer manifest on the thirteenth day. The liver and spleen were shown in Fig. 1. Additional hematologic values were a platelet count of 685,600; 13,700 leucocytes, of which 24 per cent were segmented polymorphonuclears, 71 per cent lymphocytes and 5 per cent eosinophiles; mean corpuscular volume 88 cu. μ, mean corpuscular hemoglobin 29 $\gamma\gamma$, mean corpuscular hemoglobin concentration 33 per cent. The fragility test showed beginning hemolysis at 0.48 per cent and complete hemolysis at less than 0.15 per cent, compared to a control

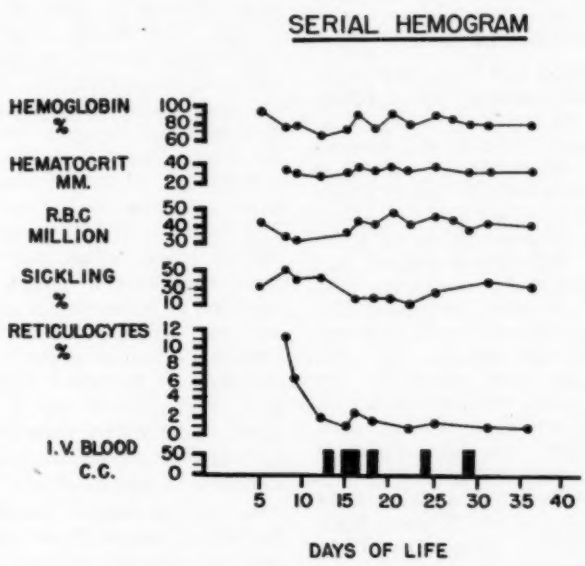

Fig. 1.

never palpable. No bleeding manifestations were noted except for the initial complaint of the mother. On the seventh day, pallor of the hands, feet, and mucous membranes was noted; and this gradually increased, reaching a peak on the thirteenth day of life. Weight gain did not begin until the ninth day of life, when it became slow and progressive. The infant's hematology was followed on samples of venous blood obtained by jugular puncture. A graphic picture of the patient's serial hemograms is with beginning hemolysis at 0.48 per cent and complete hemolysis at 0.24 per cent. The van den Bergh showed 0.5 mg. per cent direct and 0.0 mg. per cent indirect. Thymol turbidity of 1.1 units on Jan. 30, 1951. Prothrombin 18 seconds or 68 per cent. Blood group B. Rh positive. Serologic test for syphilis negative. Roentgen examinations of the skull and long bones were negative.

Six transfusions of 50 c.c. each of whole blood were given. The final transfusion was given on the twenty-

ninth day of life, and the stability of the hemogram from then till discharge on the thirty-sixth day indicated no further transfusions were necessary. Throughout her hospital stay the infant showed an adequate weight gain and exhibited no feeding problems. Her weight on discharge was 3,600 grams. The patient was discharged on an iron preparation by mouth and vitamin C and D supplements daily. She is to be followed at frequent intervals in the University Outpatient Department.

COMMENT

Various studies and controlled series have been undertaken by investigators to determine the incidence of sicklemia, or the sickle-cell trait in the general population. Representative of these studies are the results of Neel,[2] which revealed that 8 per cent of the American Negroes show the sickle-cell trait. However, of this 8 per cent, it has been mathematically computed that only one out of every forty-four persons who show the sickle-cell trait will develop sickle-cell anemia. He postulates that the gene responsible for the sickling of the erythrocyte is in a heterozygous condition if only sicklemia is present, but homozygous if the hemolytic disease is present.

Scott, Crawford, and Jenkins, from Washington, D. C.,[1] and Watson, Stahman, and Bilello,[3] from New York, have each presented a series of cases reporting the incidence of sicklemia in newborn infants. Both groups used the cover slide method for determination of sickling of the erythrocytes with capillary blood. Scott and associates[1] found a 3.4 per cent incidence of sickling in 262 infants tested. The percentage of sickling ranged from 0.5 to 40 per cent. Watson and collaborators[3] found an 8.4 per cent incidence of sicklemia in 226 newborn infants examined. The percentage of sickling in their series ranged from 0.5 per cent to 29.5 per cent. Three of the cases of sicklemia in the series of Scott and associates[1] were re-examined at 17, 11, and 7 months of age, respectively. None of these had developed sickle-cell anemia.

Prior to this report, the earliest reported age at which sickle-cell anemia has developed is the case reported by Frazier and Rice[4] in July, 1950, of a Negro infant who was diagnosed as having sickle-cell anemia on the thirty-fifth day of life, but who was admitted on the nineteenth day of life with icterus and a mild anemia, and the chief complaint of jaundice which had persisted since its onset at three days of life. The anemia progressed until transfusions became necessary on the thirty-eighth day of life. Cohen, Miller, and Orris,[5] from New York, in 1947 reported the case of a 1-month-old Puerto Rican female who died in a sickle-cell crisis, preceded and perhaps precipitated by an infection. The diagnosis of both cases seems well substantiated. Prior to that time, cases of sickle-cell anemia have been reported at 3 months of age by Wollstein and Kreidel,[6] 6 months of age by Branch,[7] 7 months of age by Anderson and Ware,[8] 9 months of age by Arena,[9] and 10 months of age by Stewart.[10] More recently two cases of sickle-cell anemia were reported in infants 3 and 7 months of age by Black,[11] in 1950.

So far as can be determined, this patient represents the earliest reported case of sickle-cell anemia. The diagnosis was confirmed by frequent laboratory examinations and history. All attempts to establish any other cause of the hemolytic anemia in this case were negative, leaving what appears to be an undeniable diagnosis of sickle-cell anemia. Although the outcome was favorable for this initial sickle-cell crisis, the prognosis for this patient must be extremely guarded because of the age of the patient. It is hoped that by reporting this case, the need for suspicion of sickle-cell anemia in crisis, in newborn infants with evidence of hemolytic anemia, will be brought to the fore.

SUMMARY

A case of sickle-cell anemia in a newborn Negro female is reported. Previous to this report the earliest reported case occurred in a 19-day-old Negro infant. Jaundice, epistaxis, and familial history prompted the suspicion of a sickle-cell crisis in this patient. Both parents showed evidence of sicklemia only, and the patient's sister, the only other living sibling, is being treated for sickle-cell anemia. The diagnosis was established by laboratory means, and other causes of hemolytic anemia excluded. Response to therapy with whole blood transfusions was gratifying. Weight gain was progressive and adequate. The need for a guarded prognosis is necessitated by the patient's age and the early onset of sickle-cell anemia.

REFERENCES

1. Scott, R. B., Crawford, R. P., and Jenkins, M.: Incidence of Sicklemia in Newborn Negro Infant, Am. J. Dis. Child. **75**: 842, 1948.
2. Neel, J. V.: The Inheritance of Sickle Cell Anemia, Science **110**: 2846, 1949.
3. Watson, J., Stahman, A. W., and Bilello, F. P.: Significance of Paucity of Sickle Cells in Newborn Negro Infants, Am. J. M. Sc. **215**: 419, 1948.
4. Frazier, C. A., and Rice, C. E.: Neonatal Sickle Cell Anemia, J. A. M. A. **143**: 1065, 1950.
5. Cohen, S. M., Miller, B. W., and Orris, H. W.: Fatal Anemia in a One-Month-Old Infant, J. PEDIAT. **30**: 468, 1947.
6. Wollstein, M., and Kreidel, K. V.: Sickle Cell Anemia, Am. J. Dis. Child. **36**: 998, 1928.
7. Branch, H. E.: Sickle Cell Anemia in a Six Month Old Colored Female Infant, J. Michigan State Med. Soc. **32**: 35, 1933.
8. Anderson, W. W., and Ware, R. L.: Sickle Cell Anemia, Am. J. Dis. Child. **44**: 1055, 1932.
9. Arena, J. M.: Cerebral Vascular Lesions, J. PEDIAT. **4**: 745, 1939.
10. Stewart, W. B.: Sickle Cell Anemia: Report With Splenectomy, Am. J. Dis. Child. **34**: 72, 1927.
11. Black, G. E.: Sickle Cell Anemia in Young Infants: Report of Two Cases, J. PEDIAT. **36**: 621, 1950.

INTRAUTERINE MENINGITIS AS A CAUSE OF HYDROCEPHALUS

R. M. N. Crosby, M.D., Wm. H. Mosberg, Jr., M.D.,* and
George W. Smith, M.D.**
Baltimore, Md.

INFECTION as an etiological agent is not usually considered in disease of the central nervous system in the newborn infant. Potter and Adair[1] observed that only sixteen deaths were attributable to infections other than syphilis in a study of 17,728 consecutive deliveries. Of these deaths, two were due to diphtheria, two to septicemia, and the remainder due to pneumonia. The same authors state in a later publication: "Infections are not common in this period, and the few which are found consist almost entirely of pneumonia."[2] In a review of 2,000 consecutive fetal or neonatal deaths,[3] Potter found infection other than syphilis in 7.9 per cent. All the infections in this series were pneumonia of either a gross or microscopic nature. Other recent authors agree upon the rarity of intrauterine infection.[4, 5, 6, 7]

In 1928 Duskes and Dodge[8] reviewed the literature concerning antenatal infection of the fetus. They found that the following infections had been reported: peritonitis of various types, pneumonia, empyema, endocarditis (although more recently Gross[9] has cast doubt on the inflammatory nature of this entity), smallpox, diphtheria, typhoid fever, anthrax, tuberculosis, scarlet fever, and bacteremias involving the respiratory, cardiovascular, and central nervous systems. Since that time a few more types of fetal infection have been reported: toxoplasmosis,[10] otitis media,[11] varicella,[12] encephalitis,[13] malaria,[14] infection with *Leptospira icterohaemorrhagicae*,[15] and gas-bacillus septicemia.[16] In this survey of the literature there was not a single proved case of intrauterine meningitis in a live birth.

The literature on meningitis of the newborn infant is not extensive and each author comments on the rarity of meningitis in the very young infant. In such an article, Babbitz and Grotts[17] describe a case of meningitis which they claim to be of antenatal origin. In support of this view the pathologist is reported to have "felt that the infection in this case occurred either at or before birth, for the lesion in the meninges was far advanced for the obvious clinical duration." It is interesting, however, that although no information is given concerning the mother's labor, the infant "appeared well" until thirty hours after birth. The organism, hemolytic streptococcus, was in all probability quite a virulent one for the baby died forty-two hours after the onset of symptoms, and the cerebrospinal fluid showed "numerous clumped white cells" and a four plus globulin reaction twelve hours before death. From the meager clinical findings given about this case it appears to be of natal origin. These authors mention a case reported by Goldreich in 1901 in which the onset was natal or neonatal, but in the original article Goldreich[18] states that the infection was probably from contaminated amniotic fluid during labor.

Because of the apparent rarity, the rather conclusive evidence of prenatal occurrence of the process and the neurosurgical implications, a case of intrauterine leptomeningitis is presented in some detail.

From the Department of Neurological Surgery, University of Maryland School of Medicine and University Hospital.

Aided by the Hoffberger Neurosurgical Fund.

*Present address: Mercy Hospital, Chicago, Ill.

**Hitchcock Fellow in Neurological Surgery.

CASE REPORT

B. S., white female, 3 days of age, was admitted to the University Hospital on Sept. 21, 1948, because of an enlarged head since before birth.

The mother of the patient first sought medical attention for her pregnancy on Feb. 16, 1948. At that time physical examination revealed no unusual findings. Her last menstrual period had been Dec. 1, 1947, and her estimated date of confinement was Oct. 8, 1948.

Fig. 1.

Fig. 2.

Past history was significant in that the only previous pregnancy, in 1946, was complicated by two episodes of vaginal bleeding and terminated at seven months by the spontaneous delivery of a stillborn, macerated fetus. The cause of fetal death was not determined.

There was no history of recent infection or of pelvic or abdominal inflammatory disease. The serologic test for syphilis was negative.

During the third month of pregnancy an impacted molar tooth was extracted without evidence of infection, and the socket healed promptly. There were intermittent upper respiratory infections throughout the entire pregnancy. These seemed to become more severe during the seventh month and persisted until delivery. In the fourth month she had a minimal amount of bloody vaginal discharge which subsequently became mucoid and was present until term. No cultures of this discharge were obtained. At no time is there known to have been any significant elevation of temperature. Throughout the entire gestational period the mother felt that fetal activity was not as vigorous or as frequent as in her first pregnancy.

Roentgen studies of the fetus were obtained during the seventh month because of the unfortunate termination of the previous pregnancy. These films were interpreted as showing a normal fetus. (Fig. 1.)

During the eighth month of pregnancy, three weeks after the x-ray studies had been made, the mother returned to her obstetrician for routine

examination. It was noted that the fetal head was overriding the symphysis pubis and that, despite the proximity of term, there was no preliminary descent or engagement of the presenting part. The fetal heartbeat was detected in the left lower abdominal quadrant and was regular with a rate of 160 per minute. The roentgenograms of the fetus were repeated at this time (Fig. 2) and it was found that the fetal head had markedly increased in size since the previous x-ray examination and was obviously "hydrocephalic."

Approximately two weeks prior to the estimated date of confinement on Sept. 17, 1948, because of the cephalopelvic disproportion, a laparotrachelotomy was performed with delivery of a full-term living female child. (Birth weight not known.)

At the time of birth the circumference of the head was 44.5 cm. and the chest 34 cm. in their greatest diameters. The over-all body length was 58.5 cm. The baby cried spontaneously and was apparently normal except for the enlarged head. The child took its feedings well and had no gastrointestinal disturbances or respiratory difficulties. There were no convulsions or spasticity noted. No fever was present. Three days after delivery the child was transferred to the University Hospital.

Physical examination on admission to the University Hospital was not unusual except for the enlarged head and abnormal facies. Rectal temperature was 98° F., pulse 120, respirations 30. The circumference of the head was 47 cm. in the plane of the greatest diameter. The lambdoidal suture was separated approximately one centimeter. The forehead was prominent, the eyes were at all times downcast, and the upper sclerae were visible.

Laboratory studies were as follows: urine, trace to one plus albumin and occasional white blood cells; hemoglobin, 118 per cent (Sahli); hematocrit, 60 mm.; sedimentation rate, 13 mm. (corrected); white blood cells 8,600, with 23 polymorphonuclear neutrophiles, 65 lymphocytes, 7 monocytes, 3 eosinophiles, and 2 myelocytes; blood urea nitrogen, 14 mg. per cent; blood sugar, 41 mg. per cent. Roentgen examination of the skull showed abnormal separation of the suture lines. The parietal and frontal bones were separated 2 cm. Electroencephalogram was compatible with increased intracranial tension. Lumbar puncture under sterile conditions was performed at 2 weeks of age with the patient in a sitting position. Initial pressure was 50 mm. of water above the occiput. The cerebrospinal fluid was xanthochromic and study of the fluid revealed 24 red blood cells and no white blood cells. The Pandy reaction was one plus, quantitative protein 123 mg. per cent, Wassermann reaction was negative, and colloidal mastic curve, 01233211.

On the first pneumoencephalogram there was poor filling due to the use of insufficient air. The films suggested an "external" hydrocephalus, but this was not definite. A ventriculogram was then done which demonstrated large quantities of air over the surface of the cerebral hemispheres as well as large, generally symmetrical ventricles without shift. (Fig. 3.)

It was not definite in either pneumogram whether the air was in the subdural or subarachnoid space, but it was felt that surgical exploration of the meninges was indicated. On Nov. 11, 1948, the anterior-superior portion of the right parietal bone was reflected. The exposed dura was of normal color but appeared tense. A small incision was made in the dura and the underlying tissue tended to extrude itself. After the aspiration of 50 c.c. xanthochromic fluid from a depth of 3 cm. the dura was opened widely, exposing a thickened, pink, opaque, vascular membrane, probably arachnoid. When this membrane was reflected, a greenish yellow, homogeneous, spongy tissue was exposed. This material was found to be present to a depth of 6.5 cm. Beneath this cerebral cortex was seen.

A. *B.* *C.*

Fig. 3.—*A*, Anteroposterior view. *B*, Posteroanterior view. *C*, Lateral view.

The yellow organizing exudate was found to be relatively avascular and pieces were removed for culture and microscopic study. The wound was then closed without drainage. A culture of this tissue yielded a pure growth of *Staphylococcus aureus hemolyticus.*

Microscopic examination of the operative specimen (Fig. 4) showed a thin membranous structure, evidently arachnoid, which had undergone extensive inflammatory change. The tissue was greatly thickened and showed a heavy infiltration of lymphocytes accompanied by numerous polymorphonuclear neutrophiles. In many areas these cells were grouped in what appeared to be large foci of liquefaction necrosis. Toward the periphery of the membrane there was abundant evidence of organization and collagen was much in evidence. Glynn stains for bacteria showed scattered gram-positive cocci, singly, and in groups of two or three but not in characteristic clumps. There was no neoplastic activity.

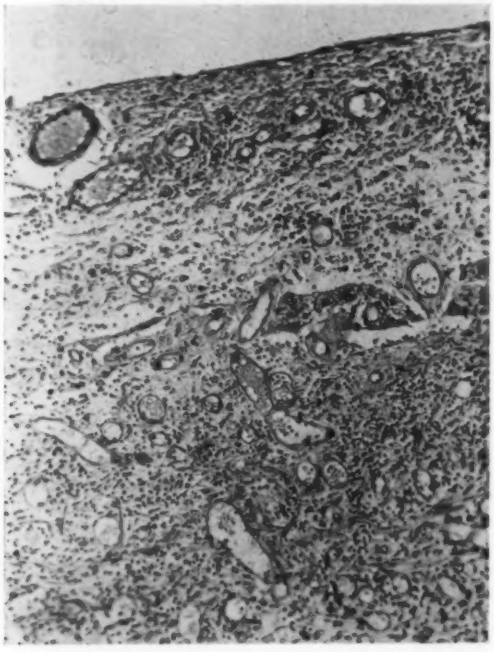

Fig. 4.

Following operation the child showed some improvement. The head gradually decreased in size although it remained large even at the time of discharge from the hospital. There was at no time any evidence of systemic infection and the child gained weight after operation. She returned home to her parents on March 19, 1949, weighing 7,500 grams, with a head measuring 45 cm. in circumference.

The patient was last seen Sept. 21, 1949. At this time the head and chest were both 52 cm. in circumference. The anterior fontanel was still open and moderately tense. The coronal suture was easily palpated and slightly separated. She was unable to support her head unaided, but the extremities were moved well. The eyes showed a

slight skew deviation at rest. The pupils were equal and reacted to light. No more than light perception could be ascertained. Her weight at this time was 10.7 kilograms. At this time the child is reported to be living but her exact physical and neurological status is not known.

DISCUSSION

The accepted modes of transmission of intrauterine infection as originally outlined by Hellendahl[19] are: through the birth canal with or without rupture of the membranes, by way of the Fallopian tubes from an intra-abdominal source, and by way of the blood stream with transplacental passage.

The transmission in this case was not one in which the rupture of the membranes or labor had any effect, since the process in the fetus was demonstrated radiologically to have been well established before term and it is reasonable to assume the same etiology of the intrauterine enlargement of the head and that present at the time of the operation. The course of the infant in the hospital showed no evidence of the onset of meningitis and the chronicity of the process as seen in the specimens taken at operation adds confirmation to the prenatal origin.

The probable mode of infection of this infant was by a transient blood stream infection in the mother with transplacental transmission. The history in this case shows ample opportunity for a maternal bacteremia but does not actually establish its occurrence. Extraction of teeth is known to be a frequent cause of bacteremia.[20] On later study of the first x-ray examination of the fetus and with the knowledge of the eventual diagnosis, the head at that time appears to have been enlarged for seven months' gestation. In all probability the meningitis began between the sixth and seventh month of pregnancy, although no specific history of maternal infection at that time can be obtained other than the upper respiratory infections mentioned.

At the time of admission this child showed nothing that would lead to the clinical diagnosis of pyogenic infection, much less leptomeningitis. The child was afebrile and had a white blood cell count of only 8,600. The cerebrospinal fluid on the original lumbar puncture at the age of 2 weeks contained no white cells and was clear and xanthochromic. The coloration of the fluid was of nonhematogenous origin.[21] It is true that the protein level of the cerebrospinal fluid was decidedly elevated, but by itself this is of little significance in the diagnosis of pyogenic leptomeningitis. No cultures were made of this fluid as there were no signs of inflammatory disease. The cerebrospinal fluid remained xanthochromic but was always clear and gave no hint concerning the inflammatory nature of the process. However, no other cell counts or cultures were made of the fluid until the time of operation.

The first air studies on the child were not conclusive but the ventriculogram (Fig. 3) demonstrated large quantities of air over the cerebral hemispheres. The dilated ventricular system was a secondary result of the improper absorption of cerebrospinal fluid. It has been shown that external hydrocephalus with distention of the cerebral subarachnoid space due to the presence of blood in the cerebrospinal fluid is one of the few forms of hydrocephalus that is curable by surgery.[22, 23] Despite the improbability of subarachnoid hemorrhage as the etiology in this case, it was felt that surgical exploration was indicated. The true diagnosis was not apparent until the meninges were explored and the yellow homogeneous inflammatory tissue was seen.

The occurrence of chronic bacterial leptomeningitis without an increase in leucocytes in the cerebrospinal fluid as recorded in the above case is unusual. It is suggested that "walling off" of the inflammatory process will allow the disappearance of leucocytes from the remainder of the cerebrospinal

fluid. This has recently been seen by one of us in a case of leptomeningitis due to *Hemophilus influenzae*. After an apparent "cure," the cerebrospinal fluid became free of organisms and leucocytes and yet aspiration through the anterior fontanel revealed xanthochromic fluid containing many cells and organisms. Although it is commonly believed that this loculated fluid is in the subdural space,[24] examination of fluid from this patient showed the pigment to be lipid in nature.[25] It was felt that lipid material had to arise from the brain tissue itself thus localizing the fluid collection to the subarachnoid rather than the subdural space. In view of the chronicity of the inflammatory process demonstrated in the operative specimen in the case above, the diagnosis of chronic pyogenic leptomeningitis without cerebrospinal fluid leucocytosis is not unreasonable.

The existence of hydrocephalus in the living newborn infant due to intrauterine leptomeningitis was new in our experience. The differential between this and hydrocephalus of other etiologies is difficult to make without surgical exploration. Despite the poor surgical result in this case, exploration should be used to be certain that a type which responds to operative therapy is not overlooked.

SUMMARY

The more recent literature concerning the occurrence of intrauterine infection of the fetus is briefly summarized. A case of hydrocephalus resulting from intrauterine infection of the meninges is reported and the evidence of its prenatal origin is discussed. The probable mode of infection and neurosurgical implications are pointed out.

We wish to thank Dr. Charles Bagley, Jr., for permission to report this case.

We are indebted to Dr. F. B. Whitworth of Cumberland, Md., for the detailed history of this case.

The pathologic material was studied by Dr. John A. Wagner.

REFERENCES

1. Potter, E. L., and Adair, F. L.: Factors Associated With Fetal and Neo-natal Deaths; Analysis of 773 Such Deaths Occurring in 17,728 Deliveries in the Chicago Lying-In Hospital, J. A. M. A. **112**: 1549, 1939.
2. Potter, E. L., and Adair, F. L.: Clinical-Pathological Study of the Infant and Fetal Mortality for a Ten-Year Period at the Chicago Lying-In Hospital, Am. J. Obst. & Gynec. **45**: 1054, 1943.
3. Potter, E. L.: Fetal and Neo-natal Deaths. A Statistical Analysis of 2000 Autopsies, J. A. M. A. **115**: 996, 1940.
4. Drillien, C. M.: Studies in Prematurity, Stillbirth and Neo-natal Death. Part III. Stillbirths and Neo-natal Deaths, J. Obst. & Gynec. Brit. Emp. **54**: 452, 1947.
5. Assali, N. S., and Zacharias, L. F.: Fetal and Maternal Mortality; an Eleven-Year Survey, Am. J. Obst. & Gynec. **54**: 651, 1947.
6. Labate, J. S.: A Study of the Causes of Fetal and Neo-natal Mortality on the Obstetrics Service at the Belleview Hospital, Am. J. Obst. & Gynec. **54**: 188, 1947.
7. Roberts, M. H.: Emergencies Encountered in the Neo-natal Period, J. A. M. A. **139**: 439, 1949.
8. Duskes, E., and Dodge, E. F.: Antenatal Infection as a Factor in Fetal Morbidity, Am. J. Dis. Child. **35**: 221, 1928.
9. Gross, P.: Concept of Fetal Endocarditis; General Review With Report of Illustrative Case, Arch. Path. **31**: 163, 1941.
10. Wolf, A., Cowen, D., and Paige, B. H.: Encephalomyelitis; Pre-natal Inception of Infantile Toxoplasmosis, Tr. Am. Neurol. A. **67**: 109, 1941.
11. Wemsath, F. A.: Intrauterine and Neonatal Otitis; Study of Seven Cases, Including Case of Otitic Meningitis, Arch. Otolaryng. **23**: 78, 1936.
12. Cosgrave, A. K., and Samuel, J.: Congenital Chicken Pox, Malayan M. J. **9**: 68, 1934.
13. Hoff, H., and Shaby, J.: Intrauterine Transmission of Encephalitis, Schweiz. Ztschr. f. allg. Path. u. Bakt. **2**: 263, 1939.
14. Das Gupta, B. M.: Malaria Infection in Placenta and Transmission to Fetus, Indian M. Gaz. **74**: 397, 1939.
15. Das Gupta, B. M.: Intrauterine Infection With Leptospira Icterohemorrhagicae, Indian M. Gaz. **74**: 28, 1939.
16. Cosgrove, S. A., and Barry, T. A.: Ante-partum Bas Bacillus Infection: Case With Septicemia and Recovery, But With Death of Fetus, New England J. Med. **222**: 344, 1940.

17. Babbitz, A., and Grotts, B. F.: Hemolytic Streptococcic Meningitis of the Newborn: Report of a Case. Arch. Pediat. **65**: 57, 1948.
18. Goldreich, L.: Meningitis beim Neugebornens, Jahrb. f. Kinderh. **56**: 808, 1901.
19. Hellendall, H.: Beitr. z. Geburtsh. u. Gynak. **10**: 320, 1906; as quoted by Slemons, J. M.: Placental Bacteremia, J. A. M. A. **65**: 1265, 1915.
20. Bartels, H. A.: Review of Recent Literature Dealing With Transient Bacteremias, Am. J. Orthodontics **26**: 366, 1940.
21. Robinson, F. H., and Miller, B. N.: On the Differentiation of Colored Cerebrospinal Fluids, Am. J. M. Sc. **191**: 538, 1936.
22. Bagley, C., Jr.: Blood in the Cerebrospinal Fluid; Resultant Functional and Organic Alterations in the Central Nervous System; Experimental and Clinical Data, Arch. Surg. **17**: 18, 1928.
23. Bagley, C., Jr., Thompson, R. K., and Crosby, R. M. N.: Distention of the Subarachnoid Space With Cerebrospinal Fluid in Infants; Enlargement of the Head and Spasticity; Surgical Correction, Ann. Surg. **129**: 662, 1949.
24. McKay, J., Jr., Morissette, R. A., Ingraham, F. D., and Matson, D. D.: Collections of Subdural Fluid Complicating Meningitis Due to Hemophilus Influenzae (Type B), New England J. Med. **242**: 20, 1950.
25. Crosby, R. M. N., and Weiland, G. S.: To be published.

Medical Progress

MANAGEMENT OF HAY FEVER IN CHILDREN, WITH SPECIAL EMPHASIS ON IMMUNIZATION (DESENSITIZATION)

BRET RATNER, M.D.
NEW YORK, N. Y.

A GREAT deal has been written on hay fever in adults, but little relative to children. There are problems in this age group that merit special consideration from the standpoint of both diagnosis and treatment. We, as pediatricians, were loathe in the past to diagnose hay fever in early childhood, but there is mounting evidence that it may occur at that period. Timely recognition and the institution of proper treatment are rewarded with favorable results.

It is quite generally accepted that hay fever is an acquired disease, and that its pathogenesis is largely concerned with the amount of exposure to a particular pollen. In those regions in which certain pollens do not exist, there is an absence of hay fever attributable to them. By the same token, an increasing incidence of pollinosis becomes evident to particular air-borne pollens indigenous to certain locales.

The following are instances of such situations:

Piness and Miller[1] cited the interesting situation of a group of city dwellers, mainly engineers, and their families, who were transferred to mountain commmunities. Thus these authors had the unique experience of studying the onset of hay fever in two comparatively young communities, the members of which were suddenly exposed to an atmosphere heavily laden with pollens that were largely different from those they had come in contact with in the past. A history of positive heredity was obtained in only 30 per cent of the cases. The great majority of the patients began to have hay fever only after moving to these vicinities, and within the first few years of their residence.

Heredity seemed to play but little part in determining the interval which elapsed between the time that residence was taken up in the community and the onset of hay fever. There were persons who had a negative family history who developed hay fever after a short residence, and, on the other hand, individuals with positive family histories did not develop hay fever until after ten to fifteen years of exposure. The authors concluded from this that a superabundance of pollen might induce sensitization irrespective of heredity. Among the patients there were a large number of children ranging in age from 1 to 10 years. This, Piness and Miller believed, was the result of an unusual contact at a particularly vulnerable period of life, rather than of an inherited susceptibility.

An even more striking example of endemic pollinosis was that studied by Phillips.[2] His paper concerns the

From the Departments of Pediatrics and Immunology, New York Medical College and Flower & Fifth Avenue Hospitals.

behavior of a group of allergic persons when they were exposed in successive years to the pollen of sugar beet which they had never before encountered. This plant was introduced into Phoenix, Arizona, in 1935, when a few experimental patches were planted. In 1936 the industry was actually introduced and 1,800 acres were planted. The following year there were 3,200 acres, and in 1938 the beet crop occupied 5,500 acres, all of which went to seed. A considerable number of individuals who were never previously sensitive to sugar beet pollen began to develop such sensitivity. Phillips concludes that about two seasons of exposure to this newly encountered pollen were required to induce clinical sensitivity.

A number of papers have appeared showing the development of sensitivity to new pollens in the Pacific zone among the members of the United States Army in the course of World War II.

It has been recognized, and confirmed by a study of Clarke and Leopold,[3] that Europeans coming to America, who have never previously suffered from ragweed hay fever, develop symptoms after an incubation period following initial contact.

That hay fever runs pari passu with civilization is known. In primordial terrains, for example, where dense forests exist there is little or no ragweed hay fever. In sections devoid of vegetation there is a like absence of ragweed hay fever. Regions, either originally thickly forested or devoid of vegetation because of climatic conditions, which are cultivated by virtue of the development of farms, gardens, lawns, golf courses, gradually change from pollen-free to ragweed pollen-rich communities. After a number of years, a certain proportion of the native population who remain in these areas develop pollen sensitivity. This all stems from the fact that many years ago the lowly ragweed was an underground weed and it was only through ploughing and cultivation that this weakly competitive plant began growing above ground. Unhampered by competition of dense vegetation for survival, this once underground weed assumed mighty proportions and became prolific, scattering its small molecular-weighted pollen grains to the winds. Pollen-free resorts lose their value as havens of freedom from symptoms when they become popular and soil cultivation begins.

Attempts are being made to curb ragweed growth by chemical sprays which cause early and rapid growth of the weed, with quick demise but little pollen formation. Even though we were to reduce its potency in highly congested areas, the winds would still carry the pollen grains from rural regions ten to twenty miles away. Nevertheless this attempt at chemical eradication of ragweed may be of some value to the communities freed by this method and it is to be hoped that with increasing awareness these efforts will be broadened.

DIAGNOSIS OF POLLEN ALLERGY IN CHILDREN

General Considerations.—Pediatrics as a specialty is often concerned with upper respiratory infections. One may be able to attribute these conditions largely to infectious agents when they occur in the winter months.

But, when children catch so-called "colds" repeatedly in the spring and summer months, some of them may be suffering from pollinosis. One of the diagnostic criteria, assuming that the cause of the upper respiratory condition may be pollens, is its seasonal recurrence. A child who repeatedly catches cold in the early spring, year after year, may be suffering from tree pollen. In the late spring or early summer, such colds may be traced to timothy, June grass, and so on, in July to plantain, and in August to ragweed and other weeds.

A differential diagnostic procedure which has been of inestimable value and which cuts corners because of its objectivity is the study of the nasal secretion by the Hansel method.[4] It is simple, direct, and vividly delineates the extent and character of the cytology present in the nasal secretions.

The child blows his nose onto waxed paper. The collected secretion is spread on a slide, and stained with Hansel's special stain, to be viewed under a microscope. No special counting is necessary, but a panoramic view of the slide discloses whether the eosinophiles are in the majority, whether neutrophiles are preponderant, or whether the secretions are mucoid and contain preponderantly epithelial cells, bacteria, or foreign material. One can then state that the nasal condition is of allergic, infectious, or irritative origin.

Whether this is absolutely foolproof, I am not prepared to say. Although the older method of viewing a thick mucopurulent exudate as infectious, and a clear watery discharge as allergic was helpful, it had its limitations and was too subjective. With this method we can, with some degree of authority, state that a nasal secretion is allergic, part allergic and part infectious, or entirely infectious in character.

An additional characteristic of allergic involvement of the nasal mucous membrane is the presence of pale boggy turbinates.

Pollen sensitivity may be manifested with no symptoms of hay fever, but with asthma as the sole allergic syndrome. When asthma is manifested during the pollinating season, year after year, even in the absence of a positive skin test, one may be justified in assuming that the etiological factor is pollen.

One must be on the qui vive to diagnose the early evidences of hay fever and to institute proper treatment. Unfortunately too many pediatricians are unwilling to concede that a distinction can be made between the infectious and allergic rhinopathies. They treat all cases of sneezing and sniffling, irrespective of their seasonal recurrence, symptomatically and brand them as bacterial infections. Tonsillectomies are suggested, antibiotics used, and antihistaminic drugs plied. I believe we should approach the problem with greater circumspection, particularly because it offers so much in the way of prevention of future difficulty for the patient. We should make our differential diagnosis with care, note the seasonal recurrence of symptoms, and not wait until asthma supervenes.

Pollen Skin Tests.—The degree of skin reactivity may be of low order in childhood pollinosis, and many children who are clinically sensitive may

show no dermal reactivity. Because of this low level of skin sensitivity the scratch test is of relatively little value in the specific diagnosis of pollen sensitivity and it is better to use the intracutaneous test. We are in the habit of testing with a 1:1,000 dilution of pollen antigen, and at times with an even greater concentration. A positive diagnosis is often established.

Kern,[5] Vaughan,[6] Kahn,[7] Peshkin,[8] and others have shown that there are patients clinically sensitive to pollens who do not react either to the scratch or intradermal test, no matter how strong a dilution is used. Peshkin recommends that the ocular test be tried, which has proved affirmative in many instances of negative skin reaction.

On the other hand, a relatively large group of children who give positive dermal reactions to pollens do not have any seasonal allergy. These children may never develop a real pollen allergy, or they may be potentially allergic. Such children should be retested each year, because skin sensitivity gradually becomes manifest and new sensitivities develop as the years go by. In this group also belong patients with eczema who give reactions to pollens, dust, and/or other inhalants, who come down with true pollen hay fever or asthma eventually.

The question arises as to therapy in these children who, on the one hand, present clinical symptoms without dermal evidence of sensitivity and, on the other hand, the second group who present no clinical symptoms of hay fever but who do have other forms of allergy and do give dermal evidence of pollen sensitivity. Kahn has suggested that the first group should be treated despite the absence of skin confirmation. It appears to me that the second group should be kept under observation and treated conservatively. However, under certain circumstances, if the attending physician is sufficiently familiar with the patient's reactivity, it may be well to institute therapy.

Another type of case that was completely baffling years ago was the child who came because of repeated respiratory episodes that reached their height in November, December, and January. History revealed in some instances that so-called "colds" actually occurred in August and recurred at the same time for one or more successive years. Upon examination, some of these patients do occasionally present sibilant and sonorous râles, not always to the degree found in asthma, but persistent enough to make one think of allergy. The testing of such a child is often rewarded by finding protein reactions to ragweed and/or other pollens, molds, and inhalants. I stress this type of case because careful perennial treatment with incriminating antigens often results in a cessation of these "colds" the following year.

Specific Diagnosis.—The specific diagnosis of the offending allergen is of utmost importance. There has been a movement on foot to divide most of our hay fever cases into two groups, i.e., the timothy-sensitive group to cover the early summer hay fevers, and the ragweed-sensitive one comprising the late summer cases. That many cases fall into these categories is undoubtedly true, but such classification does not fulfill the needs for a high enough percentage of cases.

One of the criteria for allergy is antigenic specificity, that is, specific reactivity to the pollen antigen to which the individual is sensitive. There should be a direct relationship between the pollen antigen sensitivity of the individual and his skin reactivity thereto. In experimental work on antigens, very few substances have been found with sufficient common antigenicity to encompass widely different species.

It is better to test each child, therefore, with the various pollen antigens indigenous to the area in which he resides, and also include molds, inhalants, bacteria. Thus a list may be as follows:

Trees: Oak, birch, elm, sycamore, alder, poplar, walnut, etc.
Grasses: Timothy, red top, orchard grass, sweet vernal, plantain, etc.
Weeds: Short, giant and western ragweed, cocklebur, goldenrod, mugwort, pigweed, etc.
Molds: Hormodendrum, alternaria, etc.
Bacteria: Various genera.
Epidermals and inhalants of various types.

One of the most tantaliizng experiences with children is to watch them develop new pollen sensitivities year after year. Unless one is cognizant of this, poor results will be obtained because of the incompleteness of the therapy. I am certain that one can only be rewarded with good results by the inclusion of most or all of the incriminating allergens.

It has also been contended that this or that pollen is not important because it is not found in the vicinity of the individual and that the reaction may be due to a cross antigenic factor. Whatever the validity of such an argument, it appears to me that if a positive reaction is obtained to a particular pollen, it should be included in the therapy, to enhance the antibody response.

SPECIFIC POLLEN THERAPY (DESENSITIZATION—IMMUNIZATION)

General Considerations. — Embarking upon a program of immunization against pollinosis must be well planned. Good results may on occasion be achieved the first year, but it usually takes at least two years before a satisfactory response is obtained. The number of years required to achieve permanent freedom from symptoms is not known but it has seemed wise to continue treatment for a few years. This is particularly true with children, in whom, as has been pointed out, new sensitizations may develop.

The actual basis for our present immunologic treatment cannot be definitely stated. The best thought on the subject, in my estimation, is advanced by those who present evidence that a humoral immunity, due to circulating antibodies, is established in much the same way as an immunity to bacterial endotoxins, viruses, rickettsiae, or bacterial exotoxins.

It must be granted, however, that there are antigenic differences between pollens and infectious parasites, and that there are qualitative differences between pollen antibodies and other antibodies. The capacity to invade the host and the manner of fixation to tissues of the various types of antigens differ. The most striking difference between pollens and parasites is that the former do not multiply in the host whereas the latter do. The types of exposure and periodicity of exposure show marked variations. These varying factors make one cog-

nizant of the totally different approach needed to institute a state of immunity against pollens and parasitic invaders. Were the air suddenly to be filled with clouds of streptococci, tubercle bacilli, influenza virus, or typhus rickettsiae in the same density as pollen grains, the problems concerned with infectious agents would have to be handled in much the same manner as those of pollinosis.

Pollinosis is best treated by repeated injections over a prolonged period of time. There has been much difference of opinion as to the dosage, dilution, and number of injections necessary for optimal treatment. At one time it was deemed advisable to treat a patient preseasonally and never coseasonally. At one time increasing concentrations in dosage was the rule. Some suggested treatment two or three times a week, others weekly, and others at fortnightly intervals. Since Brown's[9] recommended perennial treatment, the majority of workers have accepted it as the best mode of procedure.

One must continually bear in mind that the aim is (1) not to make the patient more hypersensitive to the pollen than he was prior to the institution of treatment, and (2) to avoid constitutional reactions.

When the offending allergens responsible for the hay fever are ascertained and each case is individualized, some patients may be found sensitive to ragweed alone, others to plantain and ragweed, still others to grasses, plantain, and ragweed. Others may be sensitive to trees alone, or in combination, others to mugwort, pigweed, cocklebur, goldenrod alone or in combination. All these combinations of pollens should be prepared as stock mixtures so that the needs of each patient are satisfied.

It is ill-advised, I believe, to treat a patient against a single pollen if he is shown to be sensitive to several. A child may be sensitive to one pollen one year and develop additional sensitivities the following year. It is wise to be alert to this eventuality in order to give the patient the optimum multiple antigenic stimulus for the development of a high titer of circulating antibodies.

If the patient is treated against certain offending pollens and not against others, symptoms will be evoked from a sensitivity to those to which no immunity has been developed.

Choice of Immunizing Agents.—If a child manifests a dermal reaction to trees, grasses, plantain, ragweed, and other pollens, he is started in the fall with a mixture containing all. After the tree season (May), the trees are deleted. After the grass season (June), they in turn are deleted. Following the plantain season (July), the ragweed and other late pollens are continued alone. This cycle is repeated the ensuing year.

If there are sensitivities to molds, inhalants, or dust, these are given in conjunction with the pollen antigens.

Dosage.—The dose ranges between 0.1 and 0.3 c.c., depending on the local reaction observed. Solutions in 1:5,000 dilution are used throughout the treatment. The concentration of the pollen mixture is not increased. This procedure is based on the fact that the immune response to a given quantity of antigen is augmented when repeated. The 1:5,000 dilution would give a certain immunologic response the first time it is injected, and

a greater response with subsequent injections of equal quantity. This of course is the well-known anamnestic or booster reaction. The maximum response is thus achieved with the minimum amount of antigen.

Restricting the quantity of injected antigen to a minimum is perhaps the soundest principle one can adopt, (1) because the smaller the amount of antigen injected, the less chance there is of augmenting the hypersensitivity of the individual, and (2) the danger of constitutional reactions is reduced.

We have successfully used this small constant dosage procedure for many years. The immunity response has been good.

This procedure was first adopted by me some fifteen years ago because of a constitutional reaction which a child had in the office. I was so fearful of increasing the dosage after that episode that I stayed within the limits of a 1:10,000 dilution for the remaining course of injections and had an excellent clinical and immunologic response. Since that time I have adhered strictly to this method. Yet the possibility of a constitutional reaction in a particular case is ever present. Hence precaution is rewarding, particularly if a good immunity response can be achieved with small doses.

I marvel at the audacity of many physicians who cast caution to the winds and still give increasing and large doses, concentrations as high as 1:100, which is called the "maintenance dose." The significance of the concept of maintenance dose is one which I have yet to learn. Rackemann[10] demonstrated the futility of this concept when he showed patient after patient manifesting constitutional reactions on a so-called "maintenance dose."

Intervals of Imunization.—Perennial treatment is adopted in all of our cases. The patient in the beginning receives injections once every week, and eventually once every two or three weeks. The same pollen mixtures are not necessarily given at each visit when the patient is coming in each week, but rather alternated with the other adjuvants.

With children who go on vacations the injections are interrupted completely for a period ranging from a few weeks to two months. Patients are requested to come in immediately upon their return to get booster doses and these are given two or three times at intervals of a few days. The regular injections are then resumed at the customary intervals. Children who do not come in promptly may develop hay fever symptoms, but after several injections they quickly become readjusted. It is extremely important therefore that they come in promptly upon return for their booster stimuli.

It is necessary to modify the procedure also in those instances in which children are brought in from a great distance. These patients come in for one or two weeks once a month, depending on their convenience. If they come in for one day, the injections are given in the morning and afternoon. If they come in for two days, the treatment can be given on successive days instead. I have several children under my care who are being treated most successfully in this fashion. This may turn out to be the ideal treatment. There must be biological differences in the immunity process which require further

evaluation before judgment is passed. I would venture to say at the moment that after two years of intensive treatment, this longer interval regimen might be tried.

Coseasonal Therapy.—The giving of injections during the pollen season has been of great concern to many allergists, for fear of inducing constitutional reactions. With a reduction of dosage during the season, minimal dosages, and the use of epinephrine, I have experienced no difficulties and continue treatment right through the season. I find also that it serves a useful purpose if the patient has any difficulties, for then advice and some medication can be given if needed.

At this point a rather common occurrence should be stressed. Treated children, who do very well when the pollen count is low, will present symptoms when the pollen count suddenly rises. If such children are given several injections at close intervals the immunity response is quickly boosted, the symptoms clear in short order, and the patients go along practically symptom-free for the remainder of the season.

Psychic Trauma From Injections.—The question is often raised of the psychic trauma which may be induced by repeated injections. Psychosomatically I should say that the immunization procedure reduces psychic trauma because children certainly do not object to the injections if they are properly administered. It is interesting to witness complete absence of fear in the majority of children if injections are given with precision, rapidly, and with a sense of humor. It is also very revealing to see the conversion of a psychically irritable allergic child to one who is happy and not irritable when his allergy is allayed.[11]

SYMPTOMATIC MEDICATION

The volume of antihistaminics dispensed not only by physicians at large but also by allergists is, in my opinion, appalling. It means that the hay fever patient is not being properly managed.

Physiologically, there is no comparison between the ultimate benefits derived from the immunization procedure as compared with so-called "antihistaminic therapy." This I have discussed in a recent article[12] from which I quote one of the conclusions. "These drugs deserve a place in our armamentarium as symptomatic remedies. My objection is that many physicians and more particularly lay people, because of the widespread publicity, feel that they are cures. Furthermore, I feel that if we lay emphasis on palliative measures we will forget what is more important, that is, measures seeking to overcome the actual hypersensitivity of the patient. It is more important to look to the fundamental and basic principle underlying allergic phenomena, than to be content with mitigating measures. The latter may have a place during the period of investigation and initial treatment of a case, but certainly we should not be satisfied with that limited aim."

One might scoff at such aspirations and say that what the allergist fears is a conquest of the disease by these drugs and "finis" to the specialty of allergy. That is basically not true. Allergy will continue despite antihistaminic therapy, for these drugs only alleviate symptoms already present. They relieve the symptomatol-

ogy of urticaria and hay fever to some degree. They give little relief in eczema or asthma.

The antihistaminic drugs, on the other hand, which affect the higher brain centers so markedly in a fair percentage of patients, are not entirely devoid of harmful psychic effects.

Medication is reduced to a minimum in patients well treated. However, if a high enough degree of immunization has not yet been achieved, medication may be necessary to reduce discomfort. A combination of the accepted drugs such as atropine, ephedrine, etc., in small doses are useful. For example:

℞ Atropine sulfate	1/500 gr.
Ephedrine sulfate	1/8 gr.
Phenobarbital	1/16 gr.
Acetyl salicylic acid	2 gr.
Magnesium oxide	½ gr.
D. T. D. in capsules.	
Sig.: One, when necessary.	

Occasionally nasal instillations of ¼ per cent Neo-Synephrine are helpful.

Phenobarbital, ¼ gr., with 5 gr. of aspirin, is helpful at night. Benadryl or Pyribenzamine or Trimeton, or any of the other antihistaminics are also useful at bedtime in severe cases, as they produce sedation and afford some nasal comfort. The antihistaminic we have found to produce fewer side effects is Neohetramine.

ANCILLARY THERAPY

Adjuvant Use of Epinephrine.—For many years I have taken the further precaution of drawing up into the same syringe with the pollen mixtures 2 minims of epinephrine (1:1,000). This enables us to accomplish two things. One is to have readily available a substance to counteract a potential constitutional reaction; and, two, the vasoconstriction caused by the epinephrine slows the absorption of the injected antigen over a period of several hours. This has the effect of converting a subcutaneous injection into an intradermal one and enhances the potency of the small amounts used.

Bacterial Vaccines and Toxoids.—Still another ancillary procedure with our hay fever children is the administration of vaccines. Children suffering from hay fever seem to develop upper respiratory infections readily, which continue on as fall and winter colds.

The plan for giving the various vaccines is not a rigid one. Diphtheria, tetanus, pertussis, typhoid, paratyphoid, influenza, and scarlet immunizations and booster doses, as well as autogenous, catarrhal, and other vaccines are given conjointly with the pollen treatments. We believe this procedure serves the dual purpose of enhancing immunity to the specific organism or toxin, and also serves as an anamnestic stimulant to the general over-all antibody response of the individual. We believe these supplementary measures enhance the immune anamnestic response toward the specific pollen as well.

Environmental Considerations.—Patients will inquire about the advisability of a change in climate. The seashore is perhaps better than inland. Places such as Long Lake in the Adirondacks and the Great Lakes regions are relatively free from pollen. Deeply wooded sections are also havens of respite. Lists of such places are generally published in newspapers each hay fever season, or information

can be obtained from various Chambers of Commerce. However, to get the greatest relief, one should have to remain in these sections throughout September, which in most instances is impractical. Hence the acquisition of immunity through judicious treatment is the best course to adopt.

A child who was quite free of symptoms came down with an attack in September. Upon questioning, we learned that she visited a farm and played in the barn which contained hay laden with pollen. Pollens may remain in enclosed rooms for many months after the season.

Automobile rides in the country during the pollinating season, particularly in an open car, may be a source of trouble. A patient reporting such an episode last year, and who was warned against it, informed me that a similar ride this year in a closed car, with the ventilating system working, was satisfactorily withstood.

Contact with chrysanthemums may induce attacks, and it is best for ragweed cases to avoid close contact with this species of flower. There is a biological relationship between ragweed, chrysanthemums, and pyrethrum. The use of Flit and other pyrethrum-containing insecticides may precipitate attacks. I have in mind an employee of an oil company who was so enamored of the value of Flit that he assiduously "Flitted" rooms regularly. On two occasions his child was thrown into anaphylactic shock by this procedure. When the child was tested she was found sensitive to pyrethrum and ragweed. It is possible that this child was made sensitive to ragweed because of inordinate contact with the pyrethrum spray during her early years. It is well to examine all insecticide labels for the presence of this ingredient.

Dietary Considerations.—For many years I have adopted the use of an acid-ash diet during the hay fever season. I believe this has some merit in the light of studies of Beckman.[13] The purpose is to render the nasal mucosa as near acid as possible. However, a well-treated patient does not require such a diet. It should only be tried on untreated children who seek advice at the height of the season.

Rowe[14] believes that during the pollen season certain individuals manifest sensitivity to foods which they can take with impunity at other times.

SUMMARY

1. Hay fever is concerned with the acquisition of pollen sensitivity and may be related to the amount of exposure to particular pollens.

2. The diagnosis of hay fever should be made early so that proper treatment can be instituted in order to avoid the development of the more serious asthma.

3. The importance of nasal eosinophilia is emphasized in differentiating hay fever from infectious rhinitis.

4. Specific allergenic sensitivity must be determined in order to arrive at an adequate program for specific therapy.

5. Specific therapy must include all the positive reacting pollens.

6. Supportive therapy and adjuvant measures are discussed.

7. The perennial method of treatment is the one of choice.

8. Small dosage therapy is advocated.

9. In order to achieve a satisfactory immunologic resistance to the sensitizing pollens, treatment must be continued over a number of years.

10. The immunization procedure, if conscientiously and comprehensively pursued, is effective in reducing or actually preventing the symptomatology of hay fever, and has the noteworthy added virtue of preventing pollen asthma.

REFERENCES

1. Piness, G., and Miller, H.: An Unusual Opportunity to Make an Allergic Study of an Entire Community With the Etiology and Results of Treatment, J. Allergy **1**: 117, 1930.
2. Phillips, E. W.: Time Required for the Production of Hay Fever by a Newly Encountered Pollen, Sugar Beet, J. Allergy **11**: 28, 1939.
3. Clarke, J. A., and Leopold, H. C.: Effect of Pollen Contact Upon the Age of Onset of Hay Fever, J. Allergy **11**: 494, 1940.
4. Hansel, F. K.: Allergy of the Nose and Paranasal Sinuses, St. Louis, 1936, The C. V. Mosby Co.
5. Kern, R. A.: Seasonal (Pollen) Hay Fever With Negative Skin Tests; Results of Treatment, Ann. Clin. Med. **5**: 371, 1926.
6. Vaughan, W. T.: Pollinosis, Constitutional and Local Factors, Arch. Int. Med. **40**: 386, 1927.
7. Kahn, I. S.: Significance of Negative Skin Tests in Pollen Hay Fever and Asthma in Infants and Young Children; Treatment, South. M. J. **21**: 559, 1928.
8. Peshkin, M. M.: XI. A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests, J. Allergy **3**: 20, 1931.
9. Brown, A.: The Perennial Treatment of Seasonal Hay Fever, J. Allergy **3**: 113, 1932.
10. Rackemann, F. M.: Pollen Tolerance: Its Bearing on Treatment of Hay Fever, J. Allergy **18**: 164, 1947.
11. Clarke, T. W.: The Part of Allergy in Childhood Neuroses, J. Child Psychology **1**: 177, 1948.
12. Ratner, B.: An Evaluation of Benadryl, Pyribenzamine, and Other So-called Antihistaminic Drugs in the Treatment of Allergy, J. PEDIAT. **30**: 583, 1947.
13. Beckman, H.: Allergy Considered as a Special Type of Alkalosis, J. Allergy **1**: 496, 1930.
14. Rowe, A. H.: Clinical Allergy, Philadelphia, 1937, Lea & Febiger.

Psychologic Aspects of Pediatrics

CEREBRAL PALSY IN CHILDREN

RUTH MORRIS BAKWIN, M.D., AND HARRY BAKWIN, M.D.
NEW YORK, N. Y.

CEREBRAL palsy is "essentially a neuromuscular disease, caused by faulty development in, or damage to, the part of the brain which has to do with the control of motor function."[1] The widely used term "crippled child" is much more inclusive. According to the New York City Survey in 1941[2] a crippled child is "an individual under 21 years of age who is so handicapped through congenital or acquired defects in the use of his limbs and body musculature as to be unable to compete on terms of equality with a normal individual of the same age." Included among crippled children are victims of poliomyelitis, tuberculosis of bones and joints, trauma, osteomyelitis, cerebral damage, tumors and, in some surveys, even cardiac and nutritional disorders.

INCIDENCE

Seven children afflicted with cerebral palsy are born yearly per 100,000 population. Of this number one dies before he reaches 6 years of age. There are about 176,000 children under 21 years of age with cerebral palsy in the United States.[3] Over 17,000 of these reside in New York State,[4] indicating a fairly even distribution throughout the country.

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center, and the Department of Pediatrics, New York Infirmary.

ETIOLOGY[5, 6]

Maternal Age.—On the average the mothers of children with cerebral palsy are older than expected. The difference varies from two to over three years in various surveys.

Birth Order.—The percentage of afflicted children is higher among first born than later born children. The incidence is slightly greater among children born after the third pregnancy.

Family Incidence.—A familial incidence exists in certain congenital cerebral defects such as iso-immunization defects, amaurotic family idiocy, tuberous sclerosis, hydrocephalus, defects associated with maternal diabetes, and so on. In the large proportion of cases, however, there is no familial incidence.

Prenatal Factors.—Denhoff[7] found in the histories of the mothers of children with cerebral palsy a high incidence of abortions, premature labors and stillbirths, and severe illness prior to pregnancy. During pregnancy many were ill with nausea, anemia, and hemorrhages.

Birth History.—Difficulties at delivery are frequent in children with cerebral palsy. Precipitate birth is also more frequent.

Neonatal History.—Cyanosis, twitching and convulsions, vomiting, crying, and sucking difficulties occur in about

two-thirds of the children with cerebral palsy.

McIntire[8] listed the frequency of the various etiological factors as follows:

	Per cent
Injury at birth, including anoxia and hemorrhage	54.6
Congenital cerebral defect	23.0
Postnatal injury to the head	5.0
Encephalitis, meningitis	4.0
Other causes	13.4

Cerebral palsy is more common in premature infants than in full-term infants. Among the reasons for this are the greater fragility of the blood vessels in the premature infant and, therefore, the greater incidence of intracranial hemorrhage and the more frequent episodes of cyanosis associated with incomplete development of the respiratory mechanism and with aspiration pneumonia.

CLINICAL EVALUATION

To be considered in the clinical evaluation of children with cerebral palsy are (a) the character and extent of the neurologic lesion, (b) the mental status, and (c) the emotional status.

Classification.—Phelps has divided the children with cerebral palsy into five types with some overlapping. The first two account for most of the cases.

1. Spasticity, owing to involvement of the cerebral cortex, 40 per cent.
2. Athetosis, resulting from injury to the basal ganglia, 40 to 45 per cent.
3. Ataxia. The lesion is in the cerebellum, 10 per cent.
4. Tremor. The lesion is in the basal ganglia, 5 per cent or less. The tremor may be intention or nonintention.
5. Rigidity. The lesion is in the basal ganglia, 5 per cent. The muscles stiffen when attempts are made to move them. Tremor and rigidity are often combined.

MENTAL FUNCTIONING

Intelligence.—According to Phelps[9] about one-third of the children with cerebral palsy are feeble-minded. Mental deficiency is most frequent in the spastic and rigid groups. Children with iso-immunization defects (kernicterus) are usually defective. It is uncommon to find a child with cerebral palsy who has superior intelligence. In the large majority the neurologic defect was present at or shortly after birth, hence the children do not form even primary action patterns normally.

The mental status of children with cerebral palsy is difficulty to estimate. Many factors aside from the cortical lesion itself may reduce mental functioning. Not infrequently the general motor disability interferes with motor development and with achievement on performance tests. The acquisition of language may be difficult owing to injury to the cortical areas which have to do with the language functions, alterations in lateral dominance made necessary by the particular type of cortical involvement with corresponding failure to establish clear-cut cerebral dominance, and life in an unstimulating environment. When, in addition, the motor disturbance affects the muscles of speech, verbal expression is slow, laborious, fatiguing and, at the same time, difficultly intelligible. Associated defects in vision and hearing are often present.

Emotional factors may be important. The disturbed emotional state of children with cerebral palsy depends on the involvement of the extrapyramidal system which has to do with emotional reactivity, the reaction of the family and society in general to the child's deficiencies, and the child's own reac-

tion to his shortcomings. To be considered also is the limited environment in which the child necessarily lives and his inability to release emotional tensions in the normal way through physical activity.

The overuse of anti-epileptic drugs may reduce mental performance.

Except when the mental impairment is severe a diagnosis of mental deficiency should be made with great caution in a child with cerebral palsy. Even after the various factors just enumerated have been carefully weighed, the possibility remains that relatively intact areas of the brain will be able to take over functions which, at the time of testing, were defective.

Intelligence Testing.—Strother[10] suggests the following steps in testing the intelligence of children with cerebral palsy: First, defects in vision, hearing, and manual coordination should be investigated. Next, language comprehension and verbal expression are tested. With this information at hand a set of tests are collected and combined to suit the particular child. In some instances standard tests, such as the Stanford-Binet, may be given if certain items are eliminated. In others, when understanding and use of language are normal, verbal tests may be used. When language comprehension is poor and speech is retarded, nonlanguage tests are more suitable. In most instances time tests are useless. When sensory or motor defects are present the examiner will have to select test items not affected by these factors. There are at present no satisfactory tests for children with both manual and speech difficulties. The evaluation of any of the abbreviated tests needs an experienced psychologist. It is best to state the results in terms of mental age rather than as I.Q. which implies an accuracy of predictability that is not justifiable under these circumstances.

When the physical handicap is severe the test procedure must be still further modified and different materials selected. It may be necessary to reword the questions so that the child can respond with a nod or gesture. As yet, no norms exist for tests altered in these ways; the value of the score, therefore, depends largely on the skill, experience, and judgment of the examiner.

School.—Children with cerebral palsy are usually considerably retarded in school. This is due, in part, to the inadequacy of educational arrangements for them. An intensive program of rehabilitation is necessary before they are ready for school. They must first of all be taught to speak or otherwise express themselves. They should be in special classes in the lower grades not only because they need extra help and equipment but also because their constant activity, grimacing, and unintelligible speech make it difficult for the nonhandicapped children to accept them in the classroom.

In a state-wide survey conducted by the New Jersey State Crippled Children's Commission[11] grade placement was as follows:

	Per cent
Advanced	1
Proper grade for age	21
Retarded one or more grades	78

Children with cerebral palsy and normal intelligence can be greatly benefited by a retraining program with the cooperation of the pediatrician and psychiatrist. Through physical therapy the child who has never moved an arm or leg properly learns what is

meant by normal movement and develops this kinesthetic sense. The occupational therapist attempts to direct the movements into useful channels such as manipulation of eating utensils, holding a pencil, and so on. It may even be necessary to teach the child to swallow properly instead of gulping his food. In all training procedures the goal set should be one which the child can be expected to attain. A considerable number of children who receive training in any special school for a reasonable amount of time can be expected to attend regular school later on.

The child with cerebral palsy needs so much training that parents are likely to forget that relaxation, recreation, and satisfaction are necessary as well. It is important to eliminate the nervous strain in learning. The child does much better with less intensive effort. Frequently physical therapy, occupational therapy, and speech therapy are started at an early age and continued for many years. These are included in the curricula of some schools but often it is necessary to take the child to a hospital or have therapists come to the home. This is time-consuming and requires considerable effort. The determined desire of parents to correct the disability is a constant reminder to the child that he is different from others.

Special Disabilities.—Speech disturbances are present in about 75 per cent of children with cerebral palsy. Some never acquire speech. One-half to three-fourths can be benefited by speech training.[12] Perlstein and Shere[13] mention as reasons for the late development of speech in children with cerebral palsy and normal intelligence the following:

1. The child does not wish to talk.
2. No one talks to him.
3. He has few social contacts.
4. He may be aphasic.
5. He may have an auditory defect.
6. Spasticity or athetosis or both may interfere with the functioning of the speech organs.

The speech of children with cerebral palsy is labored, jerky, and unrhythmic. Because of rigidity of the facial muscles articulation lacks precision and there are sound substitutions and omissions. The voice is usually pitched too high or too low owing to involvement of the muscles of the larynx. It may be further altered by impaired hearing. The child's awareness that he looks strange when he talks and his realization of the impatience of others at his slowness also influence speech.

Reading.—The child with cerebral palsy, even when mentality is normal, is frequently retarded in reading. Reading is usually taught through speech and the difficulty in speech may have hindered the child in efforts to read. Reading is limited also by the small vocabulary owing to restricted social opportunities. As a result comprehension of what is read is poor. Nevertheless, reading can be taught even when the child is unable to talk, provided the mental age is 6 years or more. Reading opens a field of experience and interest difficult for the handicapped child to attain otherwise.

Handedness.—It is difficult to determine the master hand in severely spastic children. In cases of doubtful laterality both hands may be trained, reserving definitive choice for a later age.

When the handicap is severe, as in spastic hemiplegia owing to cortical damage, the afflicted hand should not be trained to lead. Phelps[9] has ob-

served that children with right-sided hemiplegia show convulsions, mental deficiency, and behavior disturbances more often than children with left-sided hemiplegia. He attributes this to the fact that, since most children are naturally right-handed, the dominant hemisphere will be more often affected in right-sided hemiplegics than in those whose difficulty is in the left extremities. Observers are agreed that, by training for handedness during early life, the contralateral side of the brain can be made to lead or become dominant. Phelps recommends, therefore, that, in children with hemiplegia, the use of the unaffected hand and arm be encouraged so that the uninjured side of the brain will become dominant.

In ataxia where the damage is cerebellar or in athetosis where the damage is basilar it is generally safe to train the dominant hand. Nevertheless the best results are usually obtained by training the less handicapped hand to lead. This is thought to decrease difficulties in speech development, stuttering, lack of concentration, and emotional instability. It may be necessary to restrain the other hand while training for dominance.

Writing is often difficult or impossible because of spasticity and jerky movements. The typewriter may be managed more easily.

There are few reports concerning the ability of the child with cerebral palsy in special fields such as comprehension, judgment, and memory. Parents frequently refer to the excellent memories of their children. Life is not very stimulating at best and it is possible that, because of meagerness of experience, certain outstanding events are retained.

PERSONALITY

Physical deformities influence personality and behavior. There is an increased desire for attention, affection, and protection, resistance against assuming responsibility, and feelings of difference, dependence, inadequacy, and inferiority. The personality changes are not highly correlated with the severity of the handicap. More important are the attitudes in the home. Many of the emotional difficulties and social maladjustments of the handicapped are attributable, in good part, to unwise parental management. The child with a chronic illness which limits his social contacts and hinders normal emotional development often enjoys his helplessness and clings to his dependency. In addition his handicap interferes with his ability to assert himself in normal fashion. The self-confidence of the normal child rests, in part, on his opportunities for expressing his aggressive tendencies. When the normal child is, for some reason, resentful of his parents he can resolve his difficulties by physical activity and aggressive play with other children. This is impossible for the child with cerebral palsy. As a result his pent-up emotions smolder, generally accompanied by a feeling of guilt.

The personalities in the various types of cerebral palsy are said to be characteristic.[14] The spastic child has been described as "shut-in" and introverted. Fearfulness is prominent. The child holds himself tense as though in readiness to react to any disturbing influence. Fear may be induced by any outside stimulus such as loud noises, sudden jars, strange situations, meeting people. Consequently he prefers an environment devoid of excitement and stimulation. He is even

afraid of demonstrations of affection because of their effect on him. The spastic child is slow to show anger and quick to recover. He needs warning before he is brought into a new situation and consideration in every phase of handling.

The rigid child resembles the spastic in personality make-up. In general, fear is not so pronounced but it may be prominent.

The child with athetosis is without excessive fear. Stimuli in the environment may be disturbing but are quickly forgotten. He likes to be with people and is, in general, well liked. He craves attention, love, and affection. He is quick to anger and slow to recover. He is often annoyed with his own deficiencies and is subject to outbursts of rage.

The personality of the ataxic child is much like that of the athetoid. He has little fear. When he realizes that he is unable to direct a movement he becomes angry. In treatment he is annoyed when asked to make repeated efforts and he gives up quickly. He appreciates firm, quiet handling. He craves affection even more than the athetoid and he is demonstrative and out-going. He likes people and makes friends easily both with normal individuals and with the handicapped. Affection and approval are necessary in working with him.

Children with nonintention tremor resemble in personality make-up the athetoid, whereas children with intention tremor are more like the spastic, though not as fearful.

The common emotional reactions of society toward the child with cerebral palsy are the following:[15]

Curiosity, somewhat similar to the interest of persons viewing the freaks in a side show.

Pity.

Oversolicitousness. This may mask an unconscious rejection.

Mild dislike. People rarely understand why they feel as they do. They merely feel uncomfortable and ill-at-ease with handicapped persons.

Repugnance and rejection. This may be overt or concealed. It may be recognized as unreasonable but the person, even though sympathetic, may not be able to change his basic response.

Fear. This may be experienced as a vague threat. The unknown makes us feel uncertain and anxious and to many the handicapped child is a strange and unknown kind of person. Fear may also be due to uneasiness in the presence of the handicapped individual. One may be afraid that one will say or do something offensive.

Sympathetic understanding.

The emotional development of children with cerebral palsy is subject to many hazards. They live in a restricted world and receive relatively little social stimulation. Opportunity for normal give-and-take is meager as group activity is lacking or greatly limited. They tend, therefore, to become dependent, self-centered, selfish, and demanding. On the other hand they are often pushed by their parents beyond their ability to achieve, especially in learning to walk and to talk. Constant nagging to correct disabilities such as allowing the head to fall backward or keeping the mouth open makes them tense, irritable, and frustrated. In addition, the feeling, as they grow older, that they are a burden to the parents and the realization, in some instances, that they are rejected adds further to their emotional discomfort.

Many parents of children with cerebral palsy feel that they are in some way responsible for the abnormal condition. This is particularly true of the mother who thinks that her pelvic size or her condition during pregnancy was

the cause of the injury. Her guilt feeling is usually associated with overanxiety, oversolicitude, and overprotection of the child. Some parents feel that they have been unjustly treated ("how could this happen to us?") and they seek to lay the blame elsewhere. Their resentment may color their attitude toward the child and in this way further affect his personality development. Sometimes the parents blame each other and this may lead to serious family friction which adds further to the child's unhappiness.

Some parents are ashamed of their afflicted child. They may be annoyed at the constant care needed, the unattractive appearance of the child, and his inability to express himself. Acceptance by siblings is less difficult although problems arise as the siblings reach adolescence and feel called upon to make explanations to friends.

The child with cerebral palsy is often the last one in the family. The reason generally given is that the care necessary is so time-consuming and burdensome and the expense is so great that it would not be fair to have more children. Acutally the shock of having such a child and the fear of having another similar one are the principal deterrents. As a consequence these children are either only children or they are without younger siblings. Older siblings are of little use as companions since they are relatively much more mature and the gap widens each year.

Another factor influencing personality development is the fixed belief of many parents that, with training, the child can become normal or nearly so. Parents of children with poliomyelitis, impaired hearing, or visual defect learn to accept their child's disability and to build his life around it. The parent of the child with cerebral palsy stresses continual training and holds out normal standards of education, job placement, and social life if the child will only try hard enough. This, being unattainable, frustrates the child and causes dejection and unhappiness.

At first the handicapped child seems to have normal plans for growing up and to wish to live like others, accepting even the delay without too much conflict. Later, when pressed too much, when goals are too high, when success is so hard to achieve, he becomes discouraged. In addition restrictions and overprotection interfere with the pleasure which normal children obtain from achievement and increasing independence.

As the child grows older his reaction to the disability changes. A few crippled children accept their handicap cheerfully. More common reactions are (1) depression, (2) anxiety, (3) resentment, (4) resignation and indifference, (5) defiance. The severity of the handicap does not seem to determine the reaction but rather the response of others, especially parents', and the amount of frustration encountered.

Adolescence is a period of great emotional conflict owing to the child's realization that he is not equipped to face adult life with its responsibilities.[16]

A survey among adults with cerebral palsy showed the need for proper guidance during childhood.[17] A terrifying situation is created for the child by the impossibly high goal of accomplishment which many parents set. The failure of the parents to accept, realistically, the handicap and to help the child to face it realistically are potent causes for unhappiness in adult life.

MANAGEMENT

Attention to the psychologic factors discussed above is essential for the proper management of children with cerebral palsy. The parents should understand how their attitudes influence emotional development. Due regard must be given to the peculiarities of personality of the children afflicted with different types of cerebral damage. An educational campaign will help the general public to understand the plight of the child with cerebral palsy so that he may have the social and occupational opportunities which he deserves. A certain amount of state aid may be necessary but special legislation, as a sop to our conscience, is to be guarded against lest it interfere with the full development of the potentialities of the cripple.

Conditions favorable to the development of a socially acceptable personality in the child with cerebral palsy are: (1) A sustained emotional atmosphere in which the child experiences affection, friendship, and acceptance. He should be neither too dependent nor should he be expected to take too much responsibility. (2) A stable, permanent home, without moving and changing schools, which gives the handicapped individual a chance to find his own niche and to discover the things that he can do well. (3) New experiences. Life must not be too monotonous; on the other hand the child's powers of concentration may be short and his experiences few so that he may need help in adjusting to new situations. (4) Adequate scope for his abilities. Too much must not be anticipated but the handicapped person should be permitted and expected to succeed within the limits of his handicap. (5) Adequate scope for the energy present. He must not be restricted too much but the impossible should not be expected.[18]

The aim for the crippled child should be independence, courage, a sense of responsibility, and a well-developed social sense.

Just as with the normal child the most important influenee on the emotional development of the individual is the social experience in the home. The attitude of the parents will influence the attitude of friends and neighbors toward the child and his handicap.[19]

Because it takes a child with cerebral palsy a long time to carry out the simplest functions, a routine and some scheduling of activities are necessary. Sufficient time must be allowed at meals. The child should be permitted to do as much for himself as possible but fatigue or exasperation should be avoided.

Regular toilet habits should be encouraged. A special toilet seat with arms and straps may be necessary. Considerable success can be expected with patient training. Many children who are unable to talk are capable of signifying their need for the toilet.

Habits of personal cleanliness and neatness should be established. With the handles of toothbrush and comb built up so that they may be more easily grasped, some children are capable of doing a fairly good job.

Dressing and undressing are difficult for the child with cerebral palsy. Training boards with different types of fastenings, dolls and pillows for practice in putting on coats and sweaters, special clothing with zippers instead of buttons are helpful. Most children will be unable to become independent in this respect until school age or later.

Muscle education should be in the hands of competent therapists who can teach the parents how to carry on treatments at home. Co-existing conditions which also require treatment are drooling, facial grimacing, awkward speech, inability to relax tense muscles, and shambling, awkward gait. The child will require a great deal of assistance and patience from an understanding adult before these can be improved or corrected. Presenting a good general appearance is important. Without that, even normally intelligent children find social acceptance difficult.

Special equipment will help the child in maintaining proper posture. Chairs, standing tables, and skis are useful.

Toys are educational as well as recreational. Sand helps in hand and finger control. Finger painting relieves tensions. Stringing of large beads, peg boards, form boards help in coordination. Adequate rest is necessary because of the increased energy output.

Poor power of concentration and distractibility are common. In the ataxic group intense concentration may cause dizziness and nausea. The athetoid, on the other hand, may understand well what is expected but the inability to respond is a reason for loss of interest. Each child must be considered in relation to his particular type of disability.

Speech training should begin in infancy at the early babbling stage. Relaxation of the muscles of speech is necessary. This may be impossible until the child has learned to relax the entire body. Parents can help but a qualified teacher is essential in making the diagnosis and planning therapy. Each child must be considered individually. The Board of Education of the City of New York[20] has published a very helpful bulletin for parents and teachers called "Speech Training for Spastics."

Playing with other handicapped children helps the child to accept his own infirmity. He learns to live with it and to achieve some sense of social security. Nursery groups are therefore of great benefit.

Discipline is necessary. The child should be expected to conform to the family group to the extent of his ability. Because of his pathetic appearance and helplessness many parents find it difficult to be firm or to deny him anything. This attitude should be avoided. He needs as much authoritative direction as a normal child. Consistent firm guidance is important.

Home teachers are available in most large cities for children with cerebral palsy whose intelligence is normal. Unfortunately only a small amount of time can be given to each child. A further disadvantage in home-teaching is lack of companionship.

The less severely afflicted children are usually admitted to classes with other crippled children. Recently the Board of Education of New York City has added special classes for children with cerebral palsy. This seems wise as the multiple handicaps of the child with cerebral palsy makes his teaching especially difficult. In the higher grades, and after adequate physiotherapy, some of these children can succeed in regular classes.

OCCUPATIONAL OPPORTUNITIES

Occupational opportunities are few for adults with cerebral palsy. Most of them are so handicapped that special equipment may be necessary. Job analysis and direct assistance are provided by some employment services.

REFERENCES

1. Watkins, M.: The Value of the Early Recognition and Early Therapy in Cerebral Palsy, J. Am. M. Women's A. 4: 48, 1949.
2. New York City Commission for the Study of Crippled Children, The Cripple Child in New York City, 1940.
3. Phelps, W. M., and Turner, A. T.: The Farthest Corner, Elyria, Ohio, 1944, National Society for Crippled Children and Adults, Inc.
4. Cerebral Palsy in New York State, New York State Cerebral Palsy Association, 1946.
5. Yannet, H.: The Etiology of Congenital Cerebral Palsy, J. PEDIAT. 24: 38, 1944.
6. Penrose, L.: Mental Deficiency, New York, 1934, Farrar and Rinehart, Inc.
7. Denhoff, E.: Diagnostic Techniques for Children With Cerebral Palsy, Rhode Island M. J. 32: 483, 1949.
8. McIntire, J. T.: The Incidence of Feeblemindedness in the Cerebral Palsied, Am. J. Ment. Deficiency 50: 491, 1946.
9. Phelps, W. M.: Paralytic Disorders, Cerebral Palsy, in Nelson New Loose-Leaf Surgery, vol. 3, New York, 1947, Thos. Nelson & Sons, p. 1800.
10. Strother, C. R.: Evaluating Intelligence of Children Handicapped by Cerebral Palsy, The Crippled Child 23: 82, 1945.
11. New Jersey State Crippled Children's Commission, Report, Trenton, N. J., 1932.
12. Pusitz, M. E.: Speech Correction in Cerebral Palsies, J. Speech Disorders 4: 209, 1939.
13. Perlstein, M. A., and Shere, M.: Speech Therapy for Children With Cerebral Palsy, Am. J. Dis. Child. 72: 389, 1946.
14. Egel, P. F.: Technique of Treatment for the Cerebral Palsy Child, St. Louis, 1948, The C. V. Mosby Co.
15. Menninger, W. C.: Emotional Adjustments for the Handicapped, The Crippled Child. 27: 4, 1949.
16. Rogers, G. G., and Thomas, L. C.: Emotional Adjustment of the Spastic Child, The Crippled Child 16: 62, 1938.
17. Odoroff, M. E.: Solving Emotional Problems, The Crippled Child 24: 21, 1946.
18. Saslow, G.: Pattern for Behavior, The Crippled Child 24: 17, 1946.
19. Allen, F. H., and Pearson, G. H. J.: The Emotional Problems of the Physically Handicapped Child, Brit. J. M. Psychol. 8: 212, 1928.
20. Speech Training for Spastics, Board of Education of the City of New York, Curriculum Bulletin 5: 1945-46 series.

Comments on Current Literature

CAT-SCRATCH FEVER

THE household pet, by sharing man's environment, also shares his diseases and parasites, and thereby serves as a potential reservoir-host for certain human maladies as well as the diseases peculiar to its own species. The domestic cat is particularly important in this regard, since this feline pet, while enjoying an intimate relationship with human beings and their environment, usually has ample opportunity for excursions outside the household and for contact with cats from other human dwellings.

In a recent issue of *The New England Journal of Medicine,* William E. R. Greer and Chester S. Keefer report a case of "Cat-Scratch Fever," a newly defined clinical entity which is acquired by man through contact with cats. They include a résumé of diseases which can be transmitted from cats to man.

While "cat-scratch fever" has been known for some time in Europe, particularly in France, the present paper is the first report of this disease to appear in the English literature. The clinical course of "cat-scratch fever" is suggestive of, but much milder than, tularemia. The authors state: "Although it is a systemic disease associated with malaise, fever, and general symptoms of an infection, the brunt of the infection is borne by lymph nodes." Exanthems may be associated with the condition, usually resembling erythema multiforme, or more rarely, as in the reported case, erythema nodosum. The disease is a self-limited one and therapy is symptomatic. Thus far, the etiology is unknown. However, an agent which produces a skin reaction is present in the pus drained from suppurative lymph nodes. After such material has been made into a skin antigen by means of the classical Frei procedure, a specific skin reaction results, following intradermal inoculation. The suggestion is made that the etiological agent may belong to the virus group.

In their case report, the authors present in detail the clinical findings and laboratory studies of a 36-year-old man who was admitted to the hospital with the chief complaints of glandular swelling in the neck and a skin rash. The history revealed that two weeks prior to admission, he awakened one morning "to find his house cat (a homeless stray cat) licking the left side of his neck in an area that contained two pimples." He was scratched on the right hand at about the same time. Four days later painless swelling of a gland on the left side of his neck was noted. The gland increased in size and the patient became progressively more ill with malaise, fever, chill, and skin rash.

Complete laboratory studies failed to disclose the nature of the infection. The involved gland eventually drained purulent material from which an antigen was prepared. When this autogenous antigen was injected intradermally, a positive reaction was observed

within twenty-four to forty-eight hours. Similar results were obtained with "cat fever" antigen which had been supplied by Dr. Lee Foshay. The patient made an uneventful recovery.

The study of this case of cat-scratch fever prompts the authors to call attention to the large number of human diseases to which cats are subjected. They point out that "present dangers of disease transmission of house cats are not well recognized." The following human diseases are found in cats: tuberculosis (bovine); tularemia; ringworm; amebiasis; diphtheria; salmonellosis (*S. enteritidis, S. anatum*); brucellosis; rabies; favus; trypanosomiasis (*T. cruzi*); leishmaniasis; creeping eruption; dog tapeworm (*D. caninum*); fish tapeworm (*D. latum*); lung-fluke disease (*P. westermani*); opisthorchiasis; schistosomiasis japonica; strongyloidiasis; spirillosis; scrub typhus.

Those diseases transmitted by cats to man are listed as follows: tularemia; rabies; rat-bite fever; feline pneumonia (virus); diphtheria; tuberculosis; brucellosis; typhus; leptospirosis (?); ringworm (*Microsporum felinum, T. circinata*); creeping eruption (*Ancylostoma braziliense*); favus (*Achorion schoenleini*); pasteurellosis; plague (?); histoplasmosis (?); cat fever.

The present report of Greer and Keefer will serve to acquaint the physician with a new clinical entity. Undoubtedly more cases of "cat-scratch fever" will be recognized, and it is anticipated that thorough investigations, including suitable virus studies, will yield clear-cut evidence of the etiology.

RUSSELL J. BLATTNER

REFERENCE

1. Greer, William E. R., and Keefer, Chester S.: Cat-Scratch Fever, New England J. Med. 244: 545-548, 1951.

News and Notes

Dr. F. H. Maurer of Peoria, Ill., died April 22, 1951.

At the 61st annual meeting of the **American Pediatric Society** held at Atlantic City, May 3 to 5, 1951, the following officers were elected for the coming year:

President: Dr. Hugh McCulloch, Chicago.
Vice-President: Dr. Arthur H. Parmelee, Beverly Hills, Calif.
Secretary-Treasurer: Dr. Aims C. McGuinness, Philadelphia.
Editor: Dr. Stewart H. Clifford, Boston.

Dr. Hattie Alexander of New York was elected to the Council.

The **Harvard Medical School** announces a Pediatric Post-Graduate Endocrinology Course at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the direction of Dr. Nathan B. Talbot and associates, Oct. 1 through 6, 1951, daily 9 A.M. to 4:30 P.M. For further details write Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston, Mass.

The **American Board of Pediatrics** will hold an examination at Buffalo, N. Y., Oct. 26, 27, and 28, 1951.

The following were certified by the **American Board of Pediatrics** at the examination at Atlantic City, N. J., May 5, 6, and 7, 1951.

Dr. Milton R. Aisenson, 144-16 72nd Ave., Flushing, N. Y.
Dr. Daniel H. Barol, 1811 Pine St., Philadelphia 3, Pa.
Dr. John Telfer Barrett, 122 Waterman St., Providence, R. I.
Dr. Charles William Beaven, 87 29th St., Newport News, Va.
Dr. Irwin M. Bleiweiss, 1855 Grand Concourse, Bronx 53, N. Y.
Dr. George J. Cardany, 7104 Chatham Rd., Chevy Chase, Md.
Dr. Nicholas H. Chiara, 7200 Ridge Blvd., Brooklyn 9, N. Y.
Dr. Perry David Cohn, 231 Lexington Ave., Passaic, N. J.
Dr. Marie Leonore Cote, 273 Liberty St., Newburgh, N. Y.
Dr. Jess Diamond, 840 Grand Concourse, New York, N. Y.
Dr. Leonardo Vicente dos Remedios, Department of Pediatrics, New York Hospital, New York, N. Y.
Dr. George Conrad Eckhardt, Streptococceal Disease Laboratory, Warren Air Force Base, Cheyenne, Wyo.
Dr. George Y. Elson, 1801 Olney Ave., Philadelphia, Pa.
Dr. Carl William Filsinger, 109 West Maple Ave., Merchantville, N. J.
Dr. Sidney Friedman, 1740 Bainbridge St., Philadelphia 46, Pa.
Dr. Daniel E. Gelfand, 1575 Krameria St., Denver 7, Colo.
Dr. Robert Grayson, 612 71st St., Miami Beach 41, Fla.
Dr. Caryl Biren Heimer, 105 Lincoln Rd., Brooklyn 25, N. Y.
Dr. James Franklin Johnson, Department of Pediatrics, New York Hospital, New York, N. Y.
Dr. Douglas Edward Johnstone, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore 24, Md.
Dr. Robert Kaye, Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.
Dr. Werner Kornfeld, 135 South Munn Ave., East Orange, N. J.
Dr. Edward Cary Lambert, 459 Berrymen Dr., Snyder, N. Y.
Dr. Thomas Francis Xavier Lenihan, 25-03 Fairlawn Ave., Fairlawn, N. J.
Dr. Edward Levitzky, 1130 Jefferson Ave., Rahway, N. J.
Dr. Harold Raymond Mancusi-Ungaro, 480 Grove St., Upper Montclair, N. J.
Dr. Bernard Margolis, 5102 Diamond St., Philadelphia 31, Pa.
Dr. Enrique Milan, Santa Ana 18, Ocean Park, Santurce, Puerto Rico.
Dr. Bertram Wilson Miller, 169-02 32nd Ave., Flushing, N. Y.
Dr. William Clayton Morgan, Professional Bldg., Salisbury, Md.

Dr. Mary Lois Murphy, Camden Municipal Hospital, Camden, N. J.
Dr. Sidney S. Marrett, 140 Passaic Ave., Passaic, N. J.
Dr. Janice Tulchin Nightingale, 545 E. 14th St., New York, N. Y.
Dr. Donald E. Nitchman, 174 Sunnyside Rd., Scotia 2, N. Y.
Dr. Herbert Hart Pomerance, 69-49 173rd St. (Utopia Station), Flushing, N. Y.
Dr. Milton Prystowsky, Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.
Dr. Martin Francis Randolph, 345 Main St., Danbury, Conn.
Dr. Frederick C. Robbins, 300 Longwood Ave., Boston, Mass.
Dr. Dudley Albert Roberts, 124 St. Paul St., Westfield, N. J.
Dr. Raymond Saigh, 174 Ivy Lane, Teaneck, N. J.
Dr. Milton Schneider, 213-03 35th Ave., Bayside, N. Y.
Dr. Ralph Schwartz, 2017 Grand Concourse, New York, N. Y.
Dr. Allen David Shapiro, 202 Grand St., Newburgh, N. Y.
Dr. John Howland Shelley, 91-10 158th Ave., Howard Beach 14, N. Y.
Dr. Bernard J. Shuman, 2643 Pacific Ave., Atlantic City, N. J.
Dr. Hyman Soifer, 105-05 69th Ave., Forest Hills, Queens, N. Y.
Dr. William Frederick Stengel, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. David Stiles, 14 South Broadway, Irvington-on-the-Hudson, N. Y.
Dr. Veronica Elizabeth B. Tisza, 44 Bowdoin St., Cambridge, Mass.
Dr. Edward Paez Wallace, 78 Federal St., Greenfield, Mass.
Dr. Richard Storer Ward, 44 West 12th St., New York 11, N. Y.
Dr. Jerome Leonard Weinstock, 5346 Gainor Rd., Philadelphia 31, Pa.
Dr. Daniel Harris Welner, 673 Parkside Ave., Buffalo, N. Y.
Dr. Kathleen Kirk Wendell, 758 High St., Pottstown, Pa.

Book Reviews

Diabetes Guide Book for the Physician, American Diabetes Association, 1950.

This little handbook is written as an outline of treatment for the use of the general practitioner.

The most important part of the book is the section dealing with the calculation of diabetic diets. First of all, the data on which the calculations of carbohydrate value of fruits and vegetables is that of available carbohydrate in the sense first proposed by McCance, twenty years ago. Second, foods are divided into six lists: milk, vegetables, fruits, breads, meats, and fats. The vegetables are divided into two groups—the first consists of a large number of vegetables that have so little available carbohydrate that it is not worth while calculating. Most of these vegetables are the root and leafy ones. Many of them are valuable from the standpoint of vitamin A and B groups.

The second group of vegetables are those that contain many estimated at 7 grams of carbohydrate for a serving, the serving being ½ of a measuring cup. All the foods are given in amounts that equal 10 grams of available carbohydrate.

The breads include not only bread and crackers, but also those vegetables which contain higher amounts of carbohydrates, such as corn and potatoes.

All meats are included in one group, and a serving is 30 grams or 1 ounce in most instances, in some 45 grams. Included along with the meats are fish and cheese.

Finally, the fats include not only butter and margarine, but cream, mayonnaise, and oils.

This simple arrangement makes the filling of diet prescription quite easy. First of all, the milk, vegetables, and fruits are put down in amounts that represent good nutrition—there is a pint of milk for adults and a quart for children. The first list of vegetables can be taken in any desired amount and the second list, at least one serving. Fruits are given in three servings. The carbohydrate and protein in these three groups are quickly estimated in round numbers and the remaining carbohydrate is supplied by the bread list

and the protein from the protein list. Then, the fat which remains, to be filled from the fat list. The system is extremely simple and its only fault is that it lacks some accuracy. However, it makes the work of dietitians easy and probably will result in more careful estimation of diabetic diets.

The sections on use of insulin, treatment of infection, diabetic coma, and surgical complications are extremely brief, but emphasize the important principles. OLMSTED.

Streptomycin und die Behandlung hematogener Tuberkuloseformen (Streptomycin and the Treatment of Blood-borne Forms of Tuberculosis). Otto Ruziczka, Wien, 1949, Springer Verlag, 173 pages.

This is a monograph based on the work with tuberculous children at the Children's Hospital in Vienna. With the great increase in the incidence of tuberculosis among the children in Europe following World War II, ample material was available for such a study. Actually within one year, i.e., December, 1947, to December, 1948, eleven cases of miliary lung tuberculosis and fifty cases of tuberculous meningitis were collected for this work.

The first fifty-five pages of the book are devoted to the history of streptomycin, and to the reporting on the pharmacologic study of this antibiotic. The second chapter comprising thirty-three pages is given over to a review of the use of streptomycin in tuberculosis in other countries.

The remaining part of the monograph is a detailed description of the clinical work on the above-mentioned material. In this part not only the clinical but also the pathological aspects of the material under discussion receives a very thorough coverage. The results of the treatment with streptomycin are more favorable in miliary lung tuberculosis than in tuberculous meningitis. After six months of treatment and under continued observation the few cases of miliary lung tuberculosis without exception showed marked improvement, did not develop any meningeal involvement, and at the time of publication gave every reason for a good prognosis.

In the group with tuberculous meningitis the prognosis is not as favorable and it is less so in the younger age groups. While under 3 years of age only 11 per cent could be listed as clinically cured, the percentage in the age group over 9 years rises to 63 per cent.

Very much depends on the stage of the disease at which the treatment is started. While in patients where the treatment was started early, 75 per cent were clinically cured, in the later stages only 43 per cent could be helped.

This early work with streptomycin is worth reading for those who are engaged in work with tuberculosis in children. With the improvements in the quality of the antibiotics and the advancement in techniques we may hope for even better results.

ZENTAY.

Survival Under Atomic Attack. NSRB Doc. 130, U. S. Government Printing Office, Washington 25, D. C., 30 pages. Price 10 cents.

This little booklet on how to survive through an atom bomb raid should have a wide reading. It should do much to allay the panic and fears which many hold today as the results of false and vague information gathered from the sensational charts and articles which have been appearing in the magazines and newspapers. Starting with the frank statement that those near the bomb would have no hope of survival, the survival rate is one out of ten in a radius of one-half mile, a fifty-fifty chance one-half to one mile away, an eighty-five out of 100 chance one to one and one-half miles away, and practically no deaths beyond two miles. The effect and danger of blast, burns, and radiation are then discussed. Then follows advice for the individual as to what measures should be taken to survive. It is one of the best written and prepared texts we have ever come across. The language is clear and simple, and the general make-up is superior. As pediatricians we would have liked to have seen the suggestion that where there is an infant or young child in the home, a case of evaporated milk should be stored away and kept in reserve if it ever becomes likely that our cities will be subjected to an atomic bombing.

Editor's Column

IS THERE A PHYSICIAN SHORTAGE?

IS THERE a shortage of physicians to meet the medical needs of today? Will a shortage develop in the next ten years? If a shortage is present or will develop, what is the extent of the shortage? Assuming a shortage how can it best be met?

While these questions have been widely discussed by medical leaders and educators the last few years, the subject has become a matter of current public discussion. Numerous editorials have appeared in the newspapers, and only a few weeks ago some of the problems involved were discussed by Dean Murphy of the University of Kansas Medical School in an excellent article in the *Saturday Evening Post* which has aroused much general interest. It is a subject of importance to every one of the 180,000 physicians actively engaged in their profession.

In any discussion of shortage several things must be kept clear in our thinking. Are we talking about a shortage for today's ordinary peacetime needs, or a shortage that will develop some ten years hence? Or are we talking about a shortage that has developed and will continue for an indefinite period as a result of the "emergency situation" with which the country is now faced and may be facing for some years to come? The events of the past year have raised this last question and have placed a fire under what was previously more or less of an academic discussion.

* * * * *

For several years the statisticians of the Federal Security Agency have been claiming a shortage of physicians for ordinary civilian needs, and have made dire predictions of the situation that will develop by 1960. Much use of this has been made by Mr. Ewing in his campaign for a federalized national health service. On the other hand, many who have studied the subject deny that a shortage exists. That a shortage exists or will develop in a few years has been based chiefly on the physician-population ratio. Much has been made of the number of physicians graduating each year some fifty years ago when the population of the country was 75 million, and the number being graduated today when the population is 150 million, together with the decrease in the number of physicians practicing in the rural areas. Statisticians who deal in figures and units of population are likely to gloss over or ignore two fundamental factors which greatly affect the question of a physician shortage. One is the difference in the quality and ability of the physicians graduating in recent years when contrasted with those graduating forty to fifty years ago, and a second is the increased amount of medical service the individual physician of today can render.

It is true that almost as many M.D. degrees were conferred in 1900 as in 1950. In 1901 there were 5,440 M.D. degrees conferred by 159 medical schools, and in 1950 there were 5,553

degrees conferred by 72 schools. But as Dr. Pritchett of the Carnegie Foundation stated in 1910, the first group of graduates represented "an enormous overproduction of uneducated and illtrained medical practitioners." The revolution in medical education which took place between 1910 and 1930 eliminated the low-grade proprietary schools, and reduced the output of M.D.'s graduated to the low figure of 2,304 in 1922. By 1930 the number graduated each year began to climb and has ranged around the 5,000 mark in recent years. In the "accelerated" years of World War II it reached nearly 7,000 a year for four years. The important point is that the physician graduating in recent years is well trained and well educated, as contrasted with the incompetent physicians turned out by the thousands by the "diploma mills" of forty to fifty years ago. One competent, well-trained physician will render better medical care and service to the public than two incompetent men with M.D. degrees. It is not simply numbers that count or are involved in the problem of furnishing medical care.

A second factor that is ignored to a large extent in the discussion of shortage is the tremendous increase in medical services which the individual physician of today can and does render when contrasted with the practicing physician of forty or fifty years ago. Those who have practiced over a span of forty years will agree that it has probably doubled. This is entirely aside from the improvement in the character of the service he renders. It results from many factors as the increase in hospitals and hospitalization of the sick, increased ancillary personnel as nurses, laboratory technicians, and anesthetists who have relieved the physician of today from many routine time-consuming tasks, the development of preventive measures which have almost wiped out such diseases as typhoid fever and diphtheria, and the newer techniques and drugs which have reduced mortality and the severity and length of illnesses. To these must be added certain important mechanical aids as the automobile and good roads, and the widespread use of the telephone, which have reduced the wasted time of the physician many hundreds of hours a year and greatly increased the number of patients the individual physician can care for.

Thus in considering a shortage of physicians for ordinary medical needs there are factors which must be taken into account besides a ratio based on the number of physicians to units of population. The United States, incidentally, has more physicians per unit of population than any other country in the world, with the exception of Israel which has been flooded with displaced doctors from Europe. A shortage cannot be based and proved on a simple physician-population ratio.

The shortage of physicians in the rural areas will not be remedied by simply graduating more doctors. Dr. Murphy presents the problems of rural medical service very well, and further indicates the measures which must be taken to attract medical men to rural areas. A recent analysis by Dickinson of the medical situation in rural Pike County, Ill., is illuminating on this subject. He finds that the sixteen physicians now practicing in Pike County can serve more people

than the forty-two physicians who practiced in the county twenty-five to thirty years ago.

* * * * *

More urgent is the problem of a shortage due to the "emergency situation." Here again we find decided difference of opinion as to the extent of and the methods to meet a shortage. Dr. Howard Rusk, chairman of the Health Resources Advisory Committee of the National Security Resources Board, a few months ago reported the findings and estimates of his committee. The Joint Committee on Medical Education in Time of National Emergency of the Association of American Medical Colleges and the Council on Medical Education and Hospitals of the American Medical Association seriously questions whether the estimates presented by Dr. Rusk's committee should be accepted as fixed and definite goals, and has presented the reasons for their differing opinion. Dr. Rusk's committee estimates a shortage of 22,000 physicians by 1954 under the present emergency mobilization plans over and above those now in sight in our medical schools. His figures are based on a continuing increase of physicians in civilian practice to maintain the 1949 physician-population ratio of 1 to 741, some 18,500 doctors for a possible troop strength of 5,000,000 by 1954, 3,300 for civilian defense, 2,800 to fully staff our public health units, 1,800 for industry and rehabilitation, and 500 for essential teaching in the medical schools. Thus it is seen that the shortage estimated by Dr. Rusk's committee is based on continuing to expand civilian needs at a peacetime rate of expansion during a time of emergency, in addition to an exceedingly generous allowance for the Armed Services—1 physician for every 200 in service in 1951 tapering off to 1 for every 270 by 1954. To meet this situation the Rusk committee recommends that in addition to increasing the number of students, the medical schools should again adopt the accelerated teaching program used during World War II.

The Joint Committee of medical educators points out that in the emergency, by 1954, according to Dr. Rusk's committee estimates, 87 per cent of the physicians would be devoting themselves to civilian care, 9 per cent to the Armed Services, and 4 per cent to certain special needs. The Joint Committee makes the point that the statistics and methods used by the Rusk committee in reaching their conclusions and recommendations are unsatisfactory and debatable, and are based on the assumption that in the emergency period physicians must carry on as usual with no increase in their load or work, and that more effective methods of handling health needs will not be utilized. It calls attention to the fact that during World War II the physician-population ratio fell to 1:1,200 and the health of the nation improved during this time. We might cite, as examples, the fall in the maternal and infant death rates during the war years. The need for a ratio of 1:270 for the Armed Forces is questioned, and attention is drawn to the admittedly wasteful utilization of physicians in service in World War II. These, with other points, lead the Joint Committee to consider the goal of 22,000 additional physicians by 1960 to be based on assumptions that

are debatable. The Rusk committee bases its estimates on an average of 6,000 graduates each year being admitted to practice. The Association of American Medical Colleges estimates 6,500 will be graduated yearly from 1953 to 1960.

* * * * *

If the "emergency" continues until 1960 or worsens before that time, there will in all probability be a shortage of physicians and the physician-population ratio for civilian medical care will of necessity increase. Just what this ratio should be no one knows, nor can anyone categorically say just what the shortage will be as it will depend on the situation that develops. The assumption that in an emergency all civilian medical services must continue as in nonemergency times is as erroneous as one that would assume that women should remain in the home and not be utilized in essential industry. The civilian population received good if not luxurious medical care from 1942 to 1947 when thousands of physicians were in service. Our troops must receive the best possible medical care, but the Armed Services should not be wasteful in their use of physicians.

* * * * *

The question that it finally comes down to is can we increase the number of physicians to reduce a shortage without lowering the quality and training of our medical graduates. On the necessity of maintaining quality there is no difference of opinion. The formation of new medical schools will not help the emergency situation. Missouri, for example, is planning a new state-supported medical school. Even if the medical interests and politicians could agree on where it is to be located, it would not increase the number of graduates before 1958 or 1959, and then by considerably less than 1 per cent. New schools are not the answer. In the last ten years the medical schools have increased their freshman medical classes 23 per cent, which is equivalent to fifteen new schools. Further there has been more care exercised in the selection of students which has resulted in a falling attrition rate. An increased admission to the medical schools is recommended by the Joint Committee wherever it is physically and financially possible. Yale is the most recent school to announce it will increase its first-year class.

The Joint Committee has further recommended that for the majority of the medical schools during an extensive war or emergency, the curriculum extend over four twelve-month years. Since it would now appear that no general acceleration of higher education is expected at this time, the Joint Committee recommends that a vacation be permitted at present between the first and second years of the medical school course, but that changes in the national or international situation may at any moment require a revision in their recommendations.

Linked up with this question of extending medical education is the financial problem. The present income of the schools does not permit of expansion. While many of the deans of the medical schools approve of Federal aid for medical education, the attitude of the physician as represented by the American Medical Asso-

ciation prefers the meeting of the costs through voluntary gifts. Further the Commission on Financing Higher Education on May 15, 1951, issued a statement opposing Federal aid for medical education.

All in all, the question of whether or not there is a shortage of physicians, or whether a serious shortage may develop as a result of the "emergency," is a complicated one with many angles, and about which there are honest differences of opinion. Of one thing we can be certain. Nothing will be gained by increasing the number of physicians if it is brought about by the lowering of the high standards of the medical education of today.

B. S. V.

REFERENCES

Mountain, Pennell, and Berger: Bulletin 305, Federal Security Agency, United States Public Health Service, 1949.

Murphy, F. D.: Sat. Eve. Post, May 26, 1951.

Burwell, C. Sidney: New England J. Med. 244: 673 (May 3), 1951.

Rusk, Howard A.: J. A. M. A. 145: 1256 (April 21), 1951.

Report of Joint Committee on Medical Education in Time of National Emergency, J. A. M. A. 145: 1288, 1951.

Dickinson, F. G.: J. A. M. A. 145: 1260, 1951.

Editorial, J. A. M. A. 46: 376 (May 26), 1951.